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Efficacy, Tolerability and Cost Effectiveness of Disease-Modifying Antirheumatic Drugs and Biologic Agents in Rheumatoid Arthritis

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Abstract

Over the last decade, several new drugs have become available for the treatment of patients with rheumatoid arthritis. These agents include the new disease-modifying antirheumatic drug (DMARD) leflunomide and the biologic agents, tumor necrosis factor (TNF)-α antagonists and an interleukin (IL)-1 receptor antagonist.

Methotrexate is commonly used as the first DMARD, has a well documented clinical efficacy and slows radiological deterioration. Sulfasalazine appears to have similar properties, albeit to a lesser extent. Leflunomide has similar efficacy as methotrexate but it is less tolerated than sulfasalazine. The adverse effect profiles of these three drugs makes regular laboratory monitoring mandatory.

Several combination therapies with DMARDs were proven to be more effective than mono-DMARD therapy. However, until now these strategies have not been widely adopted.

TNF antagonists are potent anti-inflammatory drugs, with a rapid onset of effects compared with traditional DMARDs. The IL-1 receptor antagonist, anakinra, has an intermediate place between methotrexate and the TNF antagonists with respect to efficacy.

The adverse effects of TNF antagonists include an increased incidence of common and opportunistic infections. Thus far, anakinra has not been associated with an enhanced rate of opportunistic infections.

Some of the biologic agents have been associated with worsening heart failure and demyelinating disease. The limited long-term safety data of the biologic agents are a point of concern because, at present, an enhanced risk for malignancies, particularly lymphoma, can not be excluded.

Drug costs of traditional DMARDs are up to $US3000 per year, whereas for the biologics the yearly drug costs range between $US16 000 and >$US20 000. Cost-effectiveness analyses are necessary to determine whether or not these high costs are justified. Unfortunately, adequate, prospective, economic evaluations are not yet available. Until these become available, treatment decisions will be

based on the balance of direct costs and indirect costs and expected cost savings in the future.

In the last few decades, new pharmacological treatment modalities have been developed for rheumatoid arthritis (RA) making the disease more manageable with substantial improvement in the prospects of patients with RA.

Before the mid-1980s, patients with RA were first treated with an NSAID and later on in the treatment phase a disease-modifying antirheumatic drug (DMARD) was added according to the 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, aimed at different levels of the underlying pathophysiological processes, provides additive, perhaps synergistic, efficacy without increasing the overall adverse effects.

Recently, cytokine-specific biologic therapies (biologicals) have become available for clinical use. These agents aim at blocking either tumor necrosis factor (TNF)-α or interleukin (IL)-1, two pivotal cytokines in RA, and have shown to be the most effective antirheumatic drugs that are presently available.

In this review, we discuss the major efficacy and safety data of pivotal investigations of the DMARDs and the biologic agents. Moreover, the efficacy-safety (tolerability) ratio as well as cost-effectiveness investigations are addressed. Several DMARDs are available for use in RA (hydroxychloroquine, D-penicillamine, azathioprine, gold, ciclosporin [cyclosporine], sulfasalazine, methotrexate, leflunomide); however, we have focussed on the most commonly applied DMARDs (sulfasalazine, methotrexate and leflunomide) and the available biologic agents (infliximab, etanercept, adalimumab and anakinra).

The relevant literature was retrieved from a PubMed literature search using 'rheumatoid arthritis' as one term and the DMARDs, sulfasalazine, methotrexate and leflunomide, as well as the biologic agents, infliximab, etanercept, adalimumab and anakinra. Cost effectiveness was also used as a search term in combination with the aforementioned terms. Moreover, citations from the retrieved articles were scanned for additional studies as well as abstract books of recent rheumatology conferences. Finally, the websites of the US FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) were searched for additional information regarding the biologic agents.

1. Rheumatoid Arthritis

RA is a systemic disease with chronic joint inflammation, characterised by symmetrical pain and swelling of the joints, which affects approximately 1% of the population in the US and Europe.[1] The chronic synovitis may lead to destruction of cartilage and bone. RA has a wide clinical spectrum, which varies from mild joint symptoms to severe joint destruction, accompanied by extra-articular symptoms such as pericarditis, pulmonary involvement, vasculitis and mononeuritis multiplex.[1]

In the US, RA leads to approximately 9 million physician visits and >250 000 hospital admissions annually.[2] There is a substantial economic impact of RA, with total average medical costs of approximately $US6000–$US8500 per patient yearly.[3,4]

Yearly drug costs in the US are around $US200 for sulfasalazine, $US300–$US1200 for methotrexate and $US3000 for leflunomide. Drug costs for the biologic agents varies between approximately

$US16 000 and >$US20 000 per year, depending on the frequency and dose of administration, and the coadministration of methotrexate.[2]

In addition to drug treatment, the management of patients with RA consists of coordinated multidisciplinary care, for example, with physical and occupational therapy. Successful treatment to limit joint damage and functional loss requires early diagnosis and timely initiation of disease-modifying agents.

The pain in RA is caused by joint inflammation; therefore, NSAIDs are preferred over analgesics for pain management, in view of their anti-inflammatory effects.[5] Analgesics may be added to NSAIDs in case of insufficient pain relief. These agents do not change the course of the disease nor do they prevent joint damage. Therefore, patients with persisting disease activity require early treatment with DMARDs.[5] Evidence is accumulating that DMARDs can reduce or prevent joint destruction.[6] Active RA may cause irreversible joint destruction in the first few months of the disease. Therefore, DMARDs should be initiated early in those patients with disease activity, i.e. persisting joint pain, morning stiffness or fatigue, active arthritis or persisting elevation of the C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).[5] In general, early application of DMARDs means a start within several weeks after the first visit to the rheumatologist.

Methotrexate, sulfasalazine and leflunomide are the most commonly used conventional DMARDs.[2] Methotrexate is considered the anchor drug with a better long-term efficacy than the other conventional DMARDs.[7,8] Sulfasalazine is a good alternative, particularly for women who want to have children, as no (excess) teratogenic effects have been reported.[9] Several investigations have demonstrated that combination DMARD therapy might be more effective than mono-DMARD therapy in patients with early disease.[10]

Recently, leflunomide, a new DMARD, and biologic agents such as TNFα and IL-1 antagonists have become available for RA treatment. The biologic agents have demonstrated an impressive efficacy in RA.[11]

The place of corticosteroids is a continuing matter of debate in view of the adverse effects particularly with long-term use.[12] There is no doubt that corticosteroids rapidly and effectively suppress the inflammation in RA and their use might be justified for short-term therapy, for example for 'bridging therapy' between the initiation of DMARD therapy and its actual efficacy.[13]

2. Cost-Effectiveness, Costs-Utility and Cost-Benefit Analyses

Cost-effectiveness, costs-utility and cost-benefit analyses are important instruments in medicine because they help to quantify the health benefit of a given intervention in relation to the costs.[14] These analyses use the incremental ratio, which is defined as the difference in costs of treatments divided by the differences in treatment outcomes between two interventions.

Cost-effectiveness analyses mostly measures quantifiable health outcomes (e.g. number of patients reaching the American College of Rheumatology [ACR] response criteria) in relation to the (direct and/or indirect) cost of the treatment.

Utility, where a patient assigns a value to a particular health state, is expressed by a scale ranging from 1 (perfect health) to 0 (death). It is used for quality-of-life (QOL) assessments, for example by the Maastricht Utility Measurement Questionnaire,[15] which are used in cost-utility analyses. The quality-adjusted life-years (QALYs) are the expected life-years adjusted for quality of life.

In cost-benefit analyses, both costs and benefits are expressed in monetary terms. Costs can be divided into direct costs (i.e. the actual treatment costs: doctors and hospitals costs and medicine costs), and indirect costs (i.e. costs as a result of productivity loss and loss of wages). In addition, direct costs can

be divided into medical and non-medical costs, which is important in RA because of the high impact of non-medical costs, e.g. transportation costs to the hospital and house adjustments.

Thus far, a limited number of economic evaluations of DMARDs and biologicals have been published. The majority of these studies are discussed in this review.

3. Conventional Disease-Modifying Antirheumatic Drugs (DMARDs)

3.1 Methotrexate

Methotrexate inhibits the enzyme dihydrofolate reductase and other folate-dependent enzymes, thereby decreasing DNA, RNA and protein synthesis. This inhibition is accompanied by increased levels of adenosine. Adenosine inhibits neutrophil function and the synthesis of proinflammatory cytokines, such as TNFα and IL-6.[16,17]

Methotrexate is metabolised in the liver to active polyglutamated forms and inactive 7-hydroxymethotrexate forms and approximately 60% is bound to albumin. The elimination half-life increases with dose and ranges from 3 to 15 hours. Methotrexate and its metabolites are predominantly renally excreted by glomerular filtration and proximal tubular secretion. Hence, drugs that might impair renal function should be coadministered with caution. Probenicid is contraindicated because it inhibits the tubular excretion of methotrexate.

Methotrexate can be given orally, parenterally (subcutaneously) or intramuscularly. The bioavailability of low oral doses methotrexate (up to 10mg) is relatively high but decreases with higher doses. Hence, for a patient not responding to higher doses of methotrexate (25 mg/week) parenteral administration should be considered.[18] Methotrexate is administered once weekly, with a starting dose of 7.5mg, up to 25–30 mg/week. In The Netherlands, it is recommended to add folic or folinic acid to reduce hepatotoxicity.[19]

3.1.1 Efficacy

Methotrexate Monotherapy

Open studies in the early 1980s indicated the efficacy of methotrexate, up to 15mg per week, in patients with RA refractory to other DMARD treatments.[20-22] This efficacy of methotrexate was confirmed in placebo-controlled studies investigating dosages up to 25mg per week.[23-26] A meta-analysis of these investigations showed that patients treated with methotrexate had a 39% reduction in painful joints and 29% reduction in swollen joints compared with those treated with placebo.[27,28]

Long-term observational studies with follow-up periods of >10 years showed long-lasting effectiveness with low discontinuation rates, with drug survival rates of >5 years in approximately 60% of patients, which compares favourably with the 25% reported for other DMARDs.[28] Moreover, from these studies it appears that methotrexate slows the radiological deterioration, particularly in those in whom a good clinical efficacy is achieved.

Methotrexate Combination Therapy

Thus far, five comparative trials have been published investigating combination therapy of sulfasalazine and methotrexate.[29-33] One trial indicated that triple therapy consisting of sulfasalazine, methotrexate and hydroxychloroquine was more effective than methotrexate alone or the sulfasalazine/hydroxychloroquine combination.[30] Another comparative investigation showed no efficacy differences between sulfasalazine alone, methotrexate alone, and their combination.[31] A similar investigation yielded comparable efficacy results, although there was a trend in favour of the combination sulfasalazine/methotrexate.[32]

Two trials had a step-down approach (i.e. stopping one or more drugs).[29,33] In one study the combination sulfasalazine, methotrexate, hydroxy-

chloroquine and low-dose prednisolone was compared with the sulfasalazine alone, which could be replaced by methotrexate.[33] In the combination group, prednisolone and methotrexate could be stopped provided remission was achieved during the first year. The remission rate after 2 years was twice as high in the combination group compared with sulfasalazine alone group. Clinical improvement was also in favour of the combination group. In the other trial, termed the COBRA (Combinatietherapie Bij Reumatoide Artritis) trial, the combination of sulfasalazine, methotrexate, and initially high dose prednisolone was compared with sulfasalazine alone.[29] In this study, 156 patients with early active RA were randomised to either treatment with a combination of sulfasalazine, methotrexate and prednisolone (COBRA scheme) or treatment with sulfasalazine alone. Prednisolone and methotrexate were tapered and stopped after 28 and 40 weeks, respectively. The primary efficacy outcome measure was a composite measure comprising improvement in ESR, grip strength, tender joint count, global assessment by the observer, and improvement in functional ability. The improvement of this pooled index, at week 28, was 1.4 for the combined-treatment group and 0.8 for the sulfasalazine alone group ($p < 0.0001$) and at week 56, these figures were 1.1 versus 0.9, respectively.

At present, it is not clear whether the combination of methotrexate and sulfasalazine is superior to monotherapy with these agents. The initial addition of prednisolone improves the clinical efficacy as expected and might have long-term structural benefits.

3.1.2 Tolerability

Most of the adverse effects associated with methotrexate therapy are as a result of the antifolate activity. However, serious adverse events are rare. Long-term investigations show that up to 80% of patients show intolerability to this drug and up to 30% of patients discontinued methotrexate because of these adverse effects (table I).[34] Older patients with a compromised renal function or those with low folic acid serum levels are more susceptible to these adverse effects.[32,33] Generally, these adverse effects resolve when methotrexate is stopped.

Gastrointestinal adverse events, including nausea and vomiting, are observed in up to 50% of patients and may start within a few hours after administration and last for several days. Peptic ulcer healing is reported to be disturbed by methotrexate and it is suggested that peptic ulcers should be considered a

Table I. Adverse effects of methotrexate, sulfasalazine and leflunomide

Adverse events	Methotrexate	Sulfasalazine	Leflunomide
Gastrointestinal	Nausea, vomiting, anorexia, diarrhoea, hepatotoxicity (liver fibrosis, cirrhosis)	Nausea, dyspepsia, abdominal discomfort, hepatotoxicity	Diarrhoea, nausea, dyspepsia, abdominal pain, weight loss, liver function abnormalities
Cutaneous	Alopecia, stomatitis, rash, cutaneous vasculitis, nodulosis	Urticaria, rash, pruritus	Rash, pruritus, alopecia
Haematological	Leukopenia, pancytopenia, macrocytosis	Leukopenia and agranulocytosis, thrombocytopenia, pancytopenia, macrocytosis	Thrombocytopenia, leukopenia, eosinophilia, pancytopenia
CNS	Headache, vertigo, dizziness	Headache, dizziness	Headache, dizziness
Pulmonary	Respiratory infections, pneumonitis	Eosinophilic pneumonia	Interstitial pneumonia, reported in Japan
Other	Congenital malformations, case reports of opportunistic infections, enhanced rate of Epstein-Barr-related lymphoma, fever	Neuropathy, aseptic meningitis	Hypertension, teratogenic in animal experiments

relative contraindication for methotrexate treatment.[35]

Stomatitis and alopecia are frequently reported and lead to discontinuation in approximately 5% of patients.[32,36-39] The literature is contradictory regarding whether or not supplementation with folic or folinic acid reduces the risk of stomatitis development. Bone marrow suppression is reported to be up to 25%, mostly consisting of leukopenia and induced by interaction with NSAIDs. Pancytopenia is a rare complication but has a mortality rate of 17%.[40] Risk factors are compromised renal function, folic acid deficiency, cotrimoxazole (trimethoprim-sulfamethoxazole) treatment, and an older age.[41,42]

Methotrexate pneumonitis is a rare, but potentially fatal, complication and a patient presenting with pulmonary symptoms, such as a dry cough and shortness of breath, should be evaluated promptly, albeit that most pulmonary complications are as a result of respiratory infections.[43,44]

Liver toxicity is a problem of long-term methotrexate treatment and elevated liver enzymes are reported frequently, particularly during the start of methotrexate treatment.[45] This hepatotoxicity is mostly transient after dose reduction or folic (folinic) acid supplementation, albeit that the dose of methotrexate required to obtain a comparable efficacy is higher in those patients receiving folic acid.[19,38,46,47] Serious liver disease (i.e. severe liver fibrosis and cirrhosis) is very uncommon, thus, liver biopsies are recommended only for patients with repeatedly abnormal liver function tests.[48] Moreover, baseline liver biopsies are recommended only for those patients with a history of alcohol abuse or chronic hepatitis B or C infection.

Infections are observed in 25% of patients, predominantly upper airway and urinary tract infections and occasionally opportunistic infections have been reported.[36] The literature is contradictory regarding whether or not there is an enhanced rate of perioperative infections, although some recommend discontinuation of methotrexate 2 weeks before surgery.[43] Clearly, this problem needs to be further explored before firm recommendations can be made. Methotrexate was reported to decrease creatinine clearance, making regular monitoring of renal function mandatory.[49,50]

Congenital malformations have been reported after methotrexate treatment during the first trimester of pregnancy; therefore, contraception is advised for women who use methotrexate during the child-bearing age.[51]

Patients with RA have, *a priori*, an increased risk for developing haematological malignancies, particularly lymphoma.[52,53] During methotrexate treatment there appears to be an enhanced risk for Epstein-Barr virus-associated lymphoma,[54] which frequently comes into remission after stopping methotrexate treatment.[55,56] Methotrexate does not appear to be associated with an increased risk for other lymphoma, haematological malignancies or solid tumors.[57]

CNS adverse effects associated with methotrexate include headache, vertigo and dizziness, and are reported with an incidence of up to 35%.[34,37]

In view of the hepatoxicity and haematological adverse effects of methotrexate therapy, regular laboratory monitoring is warranted.

3.2 Sulfasalazine

Sulfasalazine consists of covalently bound sulfapyridine and 5-aminosalicylic acid. Absorption is only 20% and the majority of the drug is split in the large intestine into the separate compounds.[58] Fifty percent of the 5-aminosalicylic acid is excreted in the faeces, whereas 30% is acetylated and excreted in the urine. Sulfapyridine is detected in the blood around 4 hours after ingestion and in the liver it undergoes acetylation, hydroxylation into acetylsulfapyridine, and 5-hydroxysulfapyridine, with subsequent glucuronidation.[59]

The mode of action of sulfasalazine is still not yet (precisely) known, although it appears that sulfapyridine as well as the unchanged sulfasalazine, rather than 5-aminosalicylic acid, is the active compound in rheumatic diseases.[60] Sulfapyridine has various immunomodulatory effects, such as inhibition of prostaglandins production, inhibition of several neutrophil and lymphocyte functions, and chemotaxis. It inhibits folate dependent enzymes.[61,62]

Sulfasalazine is given orally, with a starting dosage of 500–1000 mg/day and a maintenance dosage of 2000–3000 mg/day divided over 2–3 doses per day.

3.2.1 Efficacy

Sulfasalazine Monotherapy

Many investigations and meta-analyses have clearly demonstrated the efficacy, assessed by improvement of both clinical and laboratory parameters of disease activity, of sulfasalazine in the treatment of RA. Moreover, several trials have indicated that sulfasalazine can slow radiological deterioration.[63-65] However, the clinical efficacy is less than that of methotrexate.[66] A meta-analysis involving 110 studies showed that the withdrawal rate due to a lack of efficacy was 47% for sulfasalazine and 25% for methotrexate.[67]

Sulfasalazine Combination Therapy

The efficacy of sulfasalazine combination therapy is discussed in the section Methotrexate Combination Therapy.

3.2.2 Tolerability

The most common adverse effects include gastrointestinal and CNS complaints, and occur mostly in the first 2–3 months of treatment and are dose-related (table I).[68] Frequently reported adverse effects include nausea, malaise, abdominal discomfort, dizziness and headache.[69] Minor liver enzyme increases occur occasionally and usually disappear after the drug is stopped.[70] Mucocutaneous adverse events occur in 10% of the treated patients and include skin rashes, photosensitivity, urticaria and mouth ulcers. Various haematological adverse effects have been reported with lesser frequency than the aforementioned events, these include leukopenia, thrombocytopenia, agranulocytosis and haemolysis. Cases of aplastic anemia have been described,[71] often recovering after stopping the drug.

Sulfasalazine induces a decline in sperm count and morphology, resulting in a reduced fertility in men which is reversible after discontinuation of the drug.[61] A causal relationship with teratogenicity has not been reported. There was no increased incidence of fetal abnormalities nor a reduced fertility in women treated with sulfasalazine.[72]

As previously mentioned in this section, most adverse effects occur in the first 3 months of treatment, thus, during this period, regular laboratory monitoring is warranted.

3.3 Leflunomide

Leflunomide has immunomodulating, antiproliferative and anti-inflammatory properties. The most important mode of action is inhibition of the pyrimidine biosynthesis, through inhibition of the enzyme dihydroorotate dehydrogenase, thereby causing a decreased uridine production.[73,74] Uridine is an essential for DNA, RNA and protein synthesis. In particular, cells without a 'salvage mechanism' for uridine, such as T cells, are sensitive to this inhibition.[75] In addition, leflunomide might influence signal transduction by phosphorylation of tyrosinekinases.[76-78] Moreover, leflunomide inhibits nuclear factor κB, thereby influencing apoptosis.[79] Furthermore, leflunomide inhibits expression of adhesion molecules, cytokine production and the migration of neutrophils.[80,81]

Leflunomide is a lipophilic agent. More than 98% of the active metabolite is bound to plasma proteins, hence a loading dose is recommended. Leflunomide is a prodrug and its metabolite A771726 is the therapeutic compound. A771726

undergoes enterohepatic circulation contributing to its long half-life of 15 days. About 50% is unmetabolised and excreted in the faeces. Charcoal and cholestyramine bind A771726, thereby lowering the half-life to approximately 1–2 days.[82]

3.3.1 Efficacy

Leflunomide Monotherapy

Recently, a systematic review and meta-analysis of six double-blind comparative trials with leflunomide was published.[83] Six randomised, comparative trials were included in this meta-analysis,[84-89] which included a total of 2268 patients. Of these patients, 1144 received leflunomide, 680 methotrexate, 132 sulfasalazine and 312 placebo. One of these investigations was a phase II trial[84] and two investigations were extension studies.[88,89]

Overall, the trials indicated that leflunomide was significantly superior to placebo at 6 and 12 months treatment and had a similar efficacy to that of sulfasalazine and methotrexate.[83] Although these results may indicate that the efficacy of sulfasalazine and methotrexate may be similar (contradicting findings from a study cited in section 3.2.1), conclusions regarding the efficacy of sulfasalazine versus methotrexate cannot be made as these two agents were not directly compared in this trial. There were no clinical differences between leflunomide and sulfasalazine, with the exception of improvements on the Health Assessment Questionnaire (HAQ) disability index at 6 months and the number of patients achieving the ACR 20% response (ACR20) at 24 months, which were in favour of leflunomide. The ACR20, is defined as at least a 20% improvement in tender and swollen joint count and 20% improvement in three of five of the remaining core outcome measures, that is, the patient's and physician's global assessments, the patient's assessment of pain and physical function, and one laboratory assessment of an acute-phase reactant (i.e. ESR or CRP [table I]). Similarly, ACR50 and 70 response criteria can be defined as 50% or 70% improvement, respectively.

Leflunomide had a more rapid mode of onset than methotrexate or sulfasalazine.[85,86] At 1 year, the inhibition of radiological deterioration with leflunomide was similar to that of methotrexate and sulfasalazine; however, after 24 months, leflunomide was more effective than sulfasalazine.

Combination Therapy Leflunomide and Methotrexate

The rationale for combination therapy of leflunomide with methotrexate was the simultaneous inhibition of the purine metabolism by methotrexate and the pyrimidine metabolism by leflunomide, thereby possibly more efficiently inhibiting the proliferation of inflammatory cells.

An open label investigation, in which leflunomide was added to methotrexate showed that the combination was well tolerated and efficacious in 53% of patients.[90] However, liver enzyme elevations were observed in 63% of patients. Subsequently, a 24-week double-blind, placebo-controlled investigation in RA patients with a partial response to methotrexate was conducted.[91] A total of 130 patients were treated with leflunomide and 133 were treated with placebo. Leflunomide 100 mg/day was administered for 2 days followed by 10 mg/day. This dosage could be increased to 20 mg/day in case of persistent active disease. Elevated liver enzymes were seen in 28% of patients and the authors conclude that this combination can be used safely, provided appropriate laboratory monitoring is carried out. The ACR20 response, at 24 weeks, was achieved by 46% of the leflunomide-treated patients and 20% of the placebo treated patients. The ACR70 response rates were 10% and 2% in patients receiving leflunomide and placebo, respectively.

3.3.2 Tolerability

Generally, the toxicity profile is similar to that of sulfasalazine and methotrexate, although the adverse events persist for longer because of the long

half-life of the drug. The most common adverse events observed in clinical trials leading to withdrawal from leflunomide treatment were gastrointestinal symptoms (diarrhoea, nausea, dyspepsia, abdominal pain and weight loss), allergic reactions (rash and pruritus), alopecia, hypertension and elevated transaminase levels (table II).[92]

Transient cases of thrombocytopenia, leukopenia (including neutropenia) and eosinophilia have been reported.[94] Diarrhoea can occur, but is mostly mild and often resolves within 1 week; however, in approximately 35% of patients it lasts for >1 month.[94] Leflunomide is associated with an incidence of hypertension of approximately 6–10% compared with approximately 4% for placebo, sulfasalazine or methotrexate. Drug-related hypertension occurred in approximately 2–4% of the patients treated with leflunomide compared with 2% for the comparator drugs sulfasalazine and methotrexate. New onset hypertension was reported in 2% of the patients treated with leflunomide.[85,86,88,89,95]

A retrospective investigation in 99 consecutive outpatients in whom leflunomide was started revealed a total discontinuation rate of >60% (41% because of inefficacy) probably caused by patient selection.[96] Hypertension was observed in 8% of the patients, which was significantly higher than expected from the literature. As this retrospective 'clinical practice' investigation has several methodological limitations, a prospective study of the adverse effect profile of leflunomide has been initiated, with a special focus on cardiovascular risk factors (i.e. hypertension, lipid and homocysteine metabolism). Preliminary results of this investigation revealed that leflunomide does not alter the lipid profile in patients with RA,[97] in contrast to a previous small study.[98]

Recently, there was a public statement on leflunomide from the EMEA regarding severe and serious hepatic reactions.[99] The EMEA reported a total of 296 cases of hepatic reactions (estimated patient years: 104 000) of which 129 cases were adjudicated serious, including 2 liver cirrhosis and 15 liver failures (9 of which were fatal). Hepatotoxic medications were used in 109 (78%) of the serious cases. Moreover, other risk factors for liver disease were present in 33 (27%) of the serious cases. More recently, an extensive review of the US FDA Arthritis Advisory Committee concluded that there was no consistent signal for higher rates of serious liver injury in patients treated with leflunomide compared with patients treated with methotrexate.[100] These conclusions were based on databases encompassing 16 000 patients treated with leflunomide and 37 000 with methotrexate.

To date, leflunomide has not been associated with an increased risk for malignancies. Leflunomide was found teratogenic in animal investigations,[101] therefore, it is contraindicated in women who are or may become pregnant. Women receiving leflunomide treatment who wish to become pregnant must undergo a drug-elimination procedure, otherwise it may take up to 2 years to reach plasma A 771726 metabolite concentrations <0.02 mg/L, a concentration that is thought to have minimal risk. Thus far, there are no data indicating that leflunomide is associated with an enhanced risk of male-mediated fetal adverse effects. Nevertheless, it is

Table II. American College of Rheumatology (ACR) response criteria[93]a

Outcome measure
1. Number swollen joints
2. Number tender joints
3. Physician's global assessment
4. Patient's global assessment
5. Pain
6. Functional status or physical disability
7. Acute-phase reactant (erythrocyte sedimentation rate or C-reactive protein)

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

suggested that men who would like to father a child should discontinue leflunomide and undergo a drug-elimination procedure.[102]

4. Biologic Agents

TNFα is a pivotal cytokine in the pathogenesis of RA; the inhibition of TNFα has been shown to be an effective and rapid mechanism by which to control disease activity. Although TNFα antagonists appear to be the most effective antirheumatic drugs presently available, long-term safety data are not yet available.[103]

Presently, three TNFα antagonists are available for clinical use, infliximab, etanercept and adalimumab. Infliximab is a chimeric mouse/human anti-TNFα monoclonal antibody and binds to soluble as well as membrane-bound TNFα. Infliximab is intravenously administered and after the initial infusion it is given at 2, 6 and then every 8 weeks thereafter. Etanercept consists of two human TNFα receptors linked to each other and binds to circulating as well as cell-bound TNFα molecules. Etanercept is given subcutaneously twice weekly. Adalimumab is a human immunoglobulin (Ig) G1 antibody and administered subcutaneously once every 2 weeks.

Another important cytokine in the pathogenesis of RA is IL-1. Anakinra is a human IL-1 receptor antagonist and is administered once daily, subcutaneously.

4.1 Infliximab

Infliximab was the first anti-TNF agent to be investigated in RA.[104] This antibody binds with high affinity to both membrane bound and soluble TNFα but not TNFβ (lymphotoxin).[105] Infliximab has multiple effects, including reduction of serum levels of inflammatory mediators and the expression of chemokines. It reduces lymphocyte migration into the joints of patients with RA and it might decrease angiogenesis by reducing serum levels of vascular endothelial growth factor. The volume of distribution is 0.04–0.06 L/kg and the elimination half-life is approximately 9 days. Infliximab is detected longer in the serum when administered in combination with methotrexate.[105]

4.1.1 Efficacy

In a randomised trial in 73 patients with long-standing RA, infliximab was associated with a rapid onset of efficacy, with a response being achieved at 4 weeks in 79% of patients receiving high-dose (10 mg/kg) infliximab compared with 8% of patients in the placebo group.[106] Antichimeric antibodies responses were observed in 40% of infliximab-treated patients, thus, methotrexate was given additionally in the subsequent clinical trials to reduce the formation of antibodies.

In a subsequent trial, infliximab was administered in doses of 1, 3 and 10 mg/kg, with or without weekly methotrexate.[107] Significant clinical benefit was seen with all doses, with responses up to 55% at week 26 in patients receiving the combination of infliximab plus methotrexate compared with up to 35% in patients who were treated with methotrexate alone. This trial indicated that methotrexate administration prolonged the duration of response to infliximab.

In a more recent trial, 428 patients with active long standing disease who were receiving methotrexate were randomised to either infliximab 3 or 10 mg/kg given monthly or bimonthly, or placebo.[108] At week 30, the ACR20 response criteria were, 53% and 50% for patients receiving the 3 mg/kg every 4 or 8 weeks, respectively, and 58% and 52% for those receiving 10 mg/kg every 4 or 8 weeks, respectively. In the placebo group, 20% of the patients reached the ACR20 response criteria. Although for clinical trials the ACR20 are mostly used as the primary outcome, this measure represents only a modest improvement. Hence, for clinical practice, the ACR70 response criteria are more meaningful. The ACR70 response was reached in 8% and 11% of

patients receiving 3 mg/kg every 4 or 8 weeks, respectively, and in 18% and 11% of patients receiving 10 mg/kg every 4 or 8 weeks, respectively. None of the patients in the placebo group achieved the ACR70 response criteria.

Preliminary results of a large controlled investigation (presented at the 2003 meeting of the European League Against Rheumatism held in Lisbon, Portugal) in 1049 patients with early RA indicated that infliximab plus methotrexate was more effective than methotrexate (given up to 20 mg/week) alone in preventing joint destruction and disability.[109] Patients were randomised to infliximab 3 mg/kg plus methotrexate (n = 371), infliximab 6 mg/kg plus methotrexate (n = 377), or placebo plus methotrexate (n = 291). The ACR20 response criterion was reached in 66%, 62% and 54% of patients treated with 3 mg/kg plus methotrexate, 6 mg/kg plus methotrexate, and placebo plus methotrexate, respectively. The ACR70 response criterion was reached in 33%, 37% and 21%, respectively. Progression of joint destruction in the infliximab plus methotrexate arms was significantly less in comparison with the placebo plus methotrexate arm. Naturally, the final results of this trial will be needed in order for definitive conclusions to be made. Moreover, it remains to be established to which extent the results would change if methotrexate was given in a dose of 25 mg/week which, in The Netherlands, is the dose to which a patient must fail to respond to before insurance companies will reimburse the costs of anti-TNF therapy.

4.1.2 Tolerability

Common adverse events include upper respiratory and urinary tract infections, headache, fever, dizziness, flushing, gastrointestinal complaints, liver enzyme disturbances and fatigue.[110] Occasionally haematological abnormalities, aggravation of demyelating syndromes, hypo- and hypertension, worsening of heart failure, pulmonary oedema, alopecia, myalgias and arthralgias have been reported.[110] Optical neuritis, polyneuropathy, Guillain-Barré syndrome and pancytopenia were seldom observed.[110] Moreover, infusion-related reactions, such as chills, fever, pruritus, urticaria, as well as cardiopulmonary reactions, have been reported.[110] There have also been reports of fatal, serious infections including tuberculosis and sepsis, although these are rare.[110,111] Hence, patients should be thoroughly screened for past or present tuberculosis and, if necessary, treated adequately prior to the administration of infliximab.

The above-mentioned adverse events are mostly based on the clinical trials.[107-109] It is well known that the adverse event profile in the clinical trial setting may differ significantly from that observed in clinical practice. Therefore, a prospective analysis of the adverse events profile in a clinical practice cohort was performed.[112] Preliminary data indicated an infection rate comparable to that observed in the clinical trials. However, there was a tendency for a higher prevalence of infections in the high-dose group. A total of 102 patients were treated with doses of infliximab ranging from 3 to 10 mg/kg. Methotrexate was also given to patients (median dose 10 mg/week). The follow-up was up to 18 months. In patients receiving higher doses of infliximab there were 1.69 adverse events per year versus 1.37 in patients with infliximab 3 mg/kg.

Post-marketing data of >200 000 patients revealed almost 200 cases of tuberculosis, mostly as a result of reactivation and with an extrapulmonary location in >50% of patients.[113] More than 20 cases of atypical mycobacterial infections have been reported. Approximately 80 patients with other opportunistic infections have been reported including histoplasmosis, listeriosis, *Pneumocystis jiroveci* (*carinii*) infection, aspergillosis, candidiasis, cryptococcosis and coccidioidomycosis. Pancytopenia was reported in 15 patients as well as a few cases of demyelinating disease and toxic anterior neuropathy. Forty-eight cases of lymphoma have also been

reported; however, a causal relationship is difficult to establish because patients with RA (particularly those with a high disease activity) already have an enhanced risk for the development of lymphomas.

Infliximab and Heart Failure

It has been recently reported that the development of symptomatic heart failure is associated with increased levels of TNFα; a review of several experimental studies have shown that elevated levels of TNFα are capable of inducing heart failure with concomitant left ventricular dilatation and dysfunction.[114] Therefore, theoretically, it was thought that inhibition of TNFα expression or bioavailability might be beneficial for patients with symptomatic heart failure. Unfortunately, a phase II trial with infliximab in patients with moderate to severe congestive heart failure demonstrated a higher incidence of mortality and worsened heart failure in patients treated with infliximab compared with placebo.[115] Of the 101 patients treated with infliximab, 7 died (probably as a result of heart failure; however, the cause was not explicitly stated) compared with no deaths among the 49 patients treated with placebo.

Furthermore, very recently, the US FDA published a case series of 47 patients who developed new or worsening heart failure during TNFα antagonist therapy.[116] Although, the authors of this FDA report argue that their spontaneous reports are not suitable to make causal inferences, the improvement of heart failure after cessation of anti-TNFα therapy suggests that there is indeed a causal relationship. Hence, their previous warning that patients with congestive heart failure should not be given infliximab is still warranted.[117]

4.2 Etanercept

Etanercept is a construct of two copies of the human p75 receptor and blocks the interaction between TNFα and the p55 and p75 receptors on the cell surface. Etanercept binds also to TNFβ.[118] The maximum concentration of etanercept is reached 48 hours after the subcutaneous injection and its terminal half-life is 70 hours. The volume of distribution is 0.15 L/kg and its bioavailability is 76%.[119]

4.2.1 Efficacy

The first trial of etanercept indicated a clear dose-response relationship and cessation of therapy was associated with an increase in disease activity indicating the need for continuous administration.[120] A subsequent trial, in patients with longstanding RA, confirmed these findings; after 6 months treatment, an ACR20 response was achieved by 59% of patients receiving etanercept 25mg twice weekly compared with 11% of those receiving placebo and an ACR70 response was achieved by 15% of those treated with etanercept 25mg compared with 1% of placebo recipients.[120]

The first trial investigating the combination of etanercept with methotrexate showed that, in patients with RA (mean disease duration of 13 years) who were not responding to methotrexate, the addition of etanercept 25mg twice weekly resulted in a marked clinical improvement.[121] At 6 months, 71% of the patients treated with etanercept plus methotrexate achieved the ACR20 response criteria versus 27% of the patients treated with placebo plus methotrexate ($p < 0.001$). ACR50 response criteria was achieved by 39% of patients receiving etanercept plus methotrexate compared with 3% of the patients treated with placebo plus methotrexate ($p < 0.001$). Of the patients treated with etanercept, 15% reached the ACR70 response criteria versus none of the patients treated with placebo.

Etanercept was compared with methotrexate (up to 20 mg/week) in another trial in 632 patients with early RA (defined as a disease duration <3 years).[122] Patients were either treated twice weekly with etanercept 10mg (n = 208) or 25mg (n = 207) or once weekly with methotrexate (up to 20 mg/week, n = 217) for 1 year. During the first 6 months, the proportion of patients achieving ACR20 and

ACR70 response criteria were significantly greater in the etanercept 25mg group than in the methotrexate group. However, in follow-up periods that were a duration of >6 months, the differences between the two groups were no longer significant. At 12 months, 72% of the group treated with etanercept 25mg and 65% of the group treated with methotrexate had an ACR20 response ($p = 0.62$). There were only very modest radiological deteriorations in the treatment groups at 12 months, only 1.0 and 1.6 Sharp units for the etanercept 25mg and methotrexate groups, respectively (the Sharp scale measures bony erosion and joint space narrowing and the score ranges from 0 to 398). However, patients with erosions at baseline had less progression when they were treated with etanercept compared with methotrexate. This trial was followed by a continuous open-label phase; at 2 years the ACR20 response rate was 72% for the etanercept 25mg group and 59% for the methotrexate group. The change in Sharp score was somewhat better in the etanercept 25mg group compared with the methotrexate group, 1.3 and 3.2 Sharp units, respectively.[123,124] The treatment of etanercept 25mg twice weekly for 3 years resulted in sustained benefit with a 76% ACR20 response rate and at 4 years similar results were observed.[125]

Recently, the 1-year results of a comparative double-blind trial investigating etanercept with or without methotrexate versus methotrexate alone were published.[126] After 1 year of treatment, an ACR20 score was achieved by 85% of patients treated with etanercept plus methotrexate, 76% of patients treated with etanercept alone and 75% of patients treated with methotrexate. An ACR50 response at 1 year was achieved by 69% of patients receiving combination therapy versus 48% and 43% with etanercept alone and methotrexate, respectively. ACR70 scores were achieved by 43%, 24% and 19% of the patients receiving the combination, etanercept alone and methotrexate, respectively.

Of patients treated with combination therapy, 80% experienced no radiographic progression through 1 year, compared with 68% of patients treated with etanercept alone and 57% of patients treated with methotrexate. Radiological scores indicated −0.5 Sharp units for the combination etanercept/methotrexate therapy, +0.5 Sharp units for etanercept monotherapy and +2.8 Sharp units for the methotrexate alone treatment. Altogether, these data indicate a substantial benefit of the addition of methotrexate to etanercept.

4.2.2 Tolerability

Injection site reactions such as redness, pain, swelling and itching, occur in up to 40% of patients, particularly during the first month of treatment.[127] Frequently reported adverse events include mild upper respiratory tract infections, pharyngitis, respiratory disorders, dyspepsia, abdominal discomfort and rashes.[127]

The rate of serious infections in the registration trials[127] with etanercept was not significantly increased in comparison with placebo or methotrexate. Post-marketing surveillance data of >150 000 patients reported 36 cases of tuberculosis, 11 atypical mycobacterial infections, and almost 30 other opportunistic infections including candidiasis, aspergillosis, *P. jiroveci*, cytomegalovirus, cryptococcosis, sporotrichosis, histoplasmosis and listeriosis.[128] The majority of these infections occur in patients concomitantly using corticosteroids or who have comorbid conditions, such as diabetes mellitus, making them prone to infections.

Demyelinating disease was reported in 17 cases, when >77 000 patients were treated with etanercept (>55 000 treatment years).[128] Although a firm causal relationship still has to be established, it seems prudent to avoid using etanercept in patients with demyelinating disease.

Pancytopenia and aplastic anemia have seldomly been reported, and occasionally the formation of

autoantibodies and antibodies against etanercept of unknown clinical significance has been reported.[129]

Data presented by the FDA Arthritis Advisory Committee indicate that the frequency of lymphoma associated with etanercept is higher than that which is expected in the general population, with a standardised incidence ratio of 2.31 : 1.[130] However, this is not significantly different from the standardised incidence observed in patients with RA.[130]

4.3 Adalimumab

Adalimumab is a complete human antibody against TNFα and it inhibits the binding of TNFα to the p55 and p75 receptors.[131] Adalimumab binds to soluble as well as bound TNFα but not TNFβ. Adalimumab has a volume of distribution of 4.7–6.0L and a 64% bioavailability after a single 40mg subcutaneous injection. The maximum concentration is reached after approximately 130 hours. The elimination half-life is approximately 2 weeks.

4.3.1 Efficacy

Approval of adalimumab by the FDA was based on four randomised double-blind trials (studies DE 009, DE 011, DE 019, DE 031).[132] Patients had RA according to ACR criteria, and had at least six swollen and nine tender joints and a mean disease duration of >9 years. Adalimumab was given subcutaneously with methotrexate (12.5–25 mg/week) in studies DE 009[133] and DE 019.[134] In study DE 011,[135] adalimumab was given as monotherapy and in study DE 031[136] it was used in addition to other DMARDs.

In DE 009, 271 patients with RA who had an inadequate response to methotrexate and had not responded to one or more DMARDs received one of three doses of adalimumab (20, 40 or 80mg) or placebo every 2 weeks.[133] At 24 weeks, patients receiving treatment with adalimumab 40mg every other week achieved ACR20 and 70 response rates of 65% and 24%, respectively, compared with response rates of 13% and 3% for placebo recipients, respectively.

In the study, DE 011, 544 RA patients who had not responded to therapy with at least one DMARD were treated with either adalimumab 20mg, adalimumab 40mg or placebo every 2 weeks. At 26 weeks, patients treated with adalimumab 40mg achieved ACR20 and 70 response rates of 46% and 15%, respectively, compared with respective response rates of 19% and 2% for placebo recipients.

In study DE 019, 619 RA patients with an inadequate response to methotrexate were given adalimumab 40mg every 2 weeks, adalimumab 20mg weekly or placebo. At 52 weeks, ACR20 and 70 response rates for patients receiving adalimumab 40mg every other week were 59% and 23%, respectively, compared with 24% and 5% for placebo recipients, respectively. Furthermore, this trial showed that patients who were treated with adalimumab experienced a lower rate of progression in structural damage as measured by the modified Sharp score than those treated with placebo.

In study DE 031, 636 patients with RA, who were not adequately responding to other anti-rheumatic therapies, were randomised to either adalimumab 40mg or placebo for 24 weeks. A greater proportion of patients treated with adalimumab achieved ACR20 responses (53%) compared with placebo (35%) at week 24.

Altogether these four trials clearly establish the efficacy of adalimumab in RA patients with active disease. The trial data suggest that adalimumab once every 2 weeks in combination with methotrexate is more effective than adalimumab 40mg weekly or 80mg once every 2 weeks. It is hypothesised that the inhibition of adalimumab antibody formation by methotrexate might be the reason for such results.[132]

4.3.2 Tolerability

The safety/tolerability data for adalimumab are based on a large database of 2334 patients with RA

exposed to the drug for up to 4 years (data from 20 trials),[132] as well as the prescribing information of adalimumab (version 20 December 2002). The most common adverse events associated with adalimumab include injection site reactions, upper respiratory infections, headache, rash, urinary tract infection and hypertension.[132]

Of the 1289 patients in adequate and well controlled studies, 12% developed autoantibodies (vs 7% of the placebo patients) and one developed a lupus-like syndrome.[132] A total of ten lymphomas, primarily nonHodgkin's lymphoma, were observed in adalimumab treated patients; a standardised incidence ratio (SIR) of 5.4 : 1 compared with the general population. However, RA patients, particularly those with active disease, have a higher risk of lymphoma than the general population. Therefore, the data presently available do not allow final conclusions.

Adalimumab-treated patients had more frequent serious infections than did placebo-treated patients (4.2 vs 1.9 per 100 patient-years). The most commonly affected organ systems were pulmonary, musculoskeletal, skin, gastrointestinal and genitourinary.[132]

4.4 Anakinra

Anakinra is an IL-1 receptor antagonist with the same biological properties as the human IL-1 receptor agonist. It competitively inhibits the binding of IL-1α and IL-1β to the IL-1 receptor, thereby blocking the pleiotropic effects of this proinflammatory cytokine.[137] The bioavailability of anakinra is 95% following subcutaneous injection and peak plasma concentrations are reached within 3–7 hours of administration.[138] The terminal elimination half-life is 4–7 hours. The steady-state volume of distribution is 9–15L, after an initial volume of 3L.[139]

4.4.1 Efficacy

Approval of anakinra by the FDA was based on five randomised double-blind trials involving a total of almost 3000 patients.[140] Three studies were dose-ranging trials, investigating anakinra doses from 2.5 to 150mg and from 0.04 to 2 mg/kg, as discussed in this section.

Study 990145 was a double-blind placebo-controlled trial in 501 patients with active RA who were receiving a stable dose of methotrexate (10–25 mg/week) and who had a mean duration of RA of approximately 11 years.[141] Patients were randomised to either placebo or anakinra 100mg once daily subcutaneously, in addition to methotrexate. At 6 months, the ACR20 response was achieved by 22% of placebo patients and 38% of anakinra patients. The ACR70 response was achieved by 2% of placebo recipients and 6% of anakinra patients. One investigation revealed lower radiographic deterioration for the anakinra 150mg once daily dosage in comparison with placebo.[142] However, the radiological data for anakinra 100mg are not sufficient to be conclusive.[142] The fifth investigation was a safety study and is discussed in section 4.4.2.

4.4.2 Tolerability

Study 990757 was a placebo-controlled safety investigation in 1414 RA patients who had a mean disease duration of >10 years.[143] Patients were either DMARD naive or were receiving concurrent DMARD treatment. Unlike the other investigations, patients who were prone to infection, such as those with diabetes or chronic obstructive pulmonary disease, were also included. The study included a 6-month double-blind phase followed by a 30-month open-label phase. Patients were treated with either anakinra 100mg once daily or placebo. The ratio in which patients were randomised to anakinra or placebo was 4 : 1.

During the double-blind phase, adverse events were reported by 92% of patients from each group.[143] Serious adverse events occurred in 8% of both groups. Injection site reactions, such as erythema, ecchymosis, inflammation and pain, occurred in 73% of the anakinra treated patients and 33% of the

placebo recipients. Most of these reactions were transient and of mild or moderate severity.

Infectious episodes were observed in 41% of anakinra patients and 44% of placebo patients.[143] However, serious infections occurred in 23 (2.1%) anakinra-treated patients and 1 (0.4%) placebo recipients. The predominant infections were pneumonia (10 patients) and cellulitis (3 patients). No tuberculosis or opportunistic infections were observed in this study. A total of 9 malignancies were observed, 4 (0.4%) in the anakinra group and 5 (1.8%) in the placebo group. Neutralising anti-anakinra antibodies were transient and observed in 9 patients.

In all placebo-controlled studies, 8% of anakinra treated patients had a neutropenia (vs 2% placebo patients) and the absolute neutrophil count was $>1 \times 10^9$ in 0.3% patients.[140] Headache, nausea and diarrhoea occur somewhat more frequently with anakinra compared with placebo.

Anakinra as additional therapy was investigated 58 RA patients who had active disease and were receiving etanercept.[144] There were seven severe adverse events associated with the combination of anakinra and etanercept in this study, including four infections. A larger double-blind trial in 242 patients comparing a combination of anakinra and etanercept with etanercept alone also indicated an increased risk for infections for the combination, with an incidence of 7%, and the occurrence of neutropenia.[145,146] Hence, the combination of anakinra with etanercept should not be used.

5. Cost Effectiveness

5.1 DMARD therapy

5.1.1 Leflunomide

To date only a limited number of studies investigating the cost effectiveness of leflunomide have been published. Two studies are discussed under Leflunomide versus Methotrexate[147] and section 5.1.3.[148] One retrospective analysis indicated lower costs for leflunomide compared with etanercept.[149] However, this study did not address the effectiveness of leflunomide.

Recently, a cost-effectiveness study assessing the addition of leflunomide to a 5-year strategy of conventional DMARDs in RA was published.[150] This study used a 5-year decision analysis model to compare two DMARD treatment sequences, one without leflunomide (a conventional sequence) and one with leflunomide. The conventional sequence consisted of methotrexate, followed by a combination of methotrexate and sulfasalazine, followed by a combination of methotrexate, sulfasalazine and hydroxychloroquine. In case of toxicity, patients would be changed to gold sodium aurothiomalate and finally ciclosporin. In the alternative model, leflunomide was given before gold sodium aurothiomalate. A change of treatment, within a 6-month treatment cycle, took place in case of inefficacy or (severe) adverse events.

The conventional treatment strategy in the study by Maetzel and colleagues[150] was based on a clinical practice survey among American and Canadian Rheumatologists.[151] Clinical efficacy and safety data in the study were based on a thorough literature search. Standard gamble and rating scale utilities were obtained from a placebo-controlled trial with leflunomide and methotrexate.[85] Only the direct costs were taken into account. Cost effectiveness for the DMARD strategy with leflunomide was compared with the conventional strategy, expressed as cost per additional year of ACR20 response and the cost per additional QALY. Conventional DMARD strategy, over the 5-year period, would cost $US8467, whereas the addition of leflunomide would increase these costs to $US9698 (1988 values). Patients in the leflunomide sequence would be in a state of response for 2.8 years, which is 34 days extra compared with patients receiving the conventional strategy. In other words, there is a cost-effec-

tiveness ratio of $US13 096 for each additional year of ACR20 response. The patients receiving the leflunomide strategy would gain 1 week of perfect health, that is, a cost-utility ratio of $US54 229 per rating scale QALY or $US71 998 per standard gamble QALY gained (1998 values).

Altogether, this investigation by Maetzel et al.[150] suggests that leflunomide may extend the time that patients may benefit from DMARD therapy, albeit that the price per QALY gained is quite high. Moreover, indirect costs were not taken into account and the ACR20 criteria, although useful for clinical trials, is not suitable for clinical practice. Part of these limitations will be solved by modeling studies, such as that by Welsing et al.,[152] which is ongoing and so the final results are not yet available.

Leflunomide versus Methotrexate

Maetzel et al.[147] performed an economic comparison of methotrexate and leflunomide in patients with RA. This investigation was part of a 1-year comparative double trial of methotrexate (up to 15 mg/week), leflunomide (20 mg/day) and placebo in 482 patients with active RA and a disease duration of at least 6 months. In this study, the ACR20 response criteria was achieved by 46% of the methotrexate-treated patients, 52% of the leflunomide patients and 26% of the placebo patients at the end of the study.[85] By the study end, 35% of the methotrexate and 41% of the leflunomide patients achieved an ACR success rate, defined as completing 52 weeks of treatment and achieving an ACR20 response. The direct and indirect costs were measured and utility was assessed using a rating scale (patients were asked to rate their health on a scale between perfect health [rated as 100] and death [rated as 0]) and standard gamble (patients were asked to choose between their current health state [as the certain outcome] or a gamble between death and perfect health [as the uncertain outcome]).[147] According to these utility measurements, patients receiving either leflunomide or methotrexate had a more positive perception of their health than those receiving placebo. Total costs were not statistically different between methotrexate and placebo compared with leflunomide, when monitoring and drug acquisition costs were excluded. However, with the inclusion of these costs, leflunomide was significantly more expensive than methotrexate and placebo (table III). The authors argue that as methotrexate does not lead to higher utilities the analysis is limited to a cost comparison. However, currently higher dosages (up to 35 mg/week) of methotrexate are used and these dosages might have a beneficial influence on the utilities. Unfortunately, this aspect was not further discussed by the authors.

5.1.2 Combination DMARD Therapy versus DMARD Monotherapy

Verhoeven et al.[153] conducted a cost-effectiveness and cost-utility analysis of combination DMARD therapy in patients with early RA. These researchers measured direct costs and two QOL measures, i.e. the rating scale and the standard gamble method. This investigation was part of the COBRA study which is discussed briefly under Methotrexate Combination Therapy.[29] Indirect costs were not assessed in this study but in another investigation.[154]

The mean total direct costs did not significantly differ between combination therapy (methotrexate, sulfasalazine and prednisolone) and sulfasalazine alone (table IV); although they tended to be lower for the combination group.[153] Outpatient care, inpa-

Table III. Annual costs (converted from 1999 $Can to $US) for treating rheumatoid arthritis according to treatment group[147]

Type of cost	Cost per type of treatment ($US)		
	methotrexate	leflunomide	placebo
Total[a]	876	1204	906
Direct[a]	420	530	230
Indirect	451	674	629
Drug	176	2635	0
Monitoring	410	328	38

a Excluding drug and monitoring costs.

tient care and non-healthcare each comprised one-third of the costs. Treatment costs for the combination therapy were approximately twice that of sulfasalazine alone. However, the combined treatment led to fewer hospital admissions and in-hospital days, and consequently lower direct costs when excluding drug and monitoring costs. At week 28, both rating scale and standard gamble utility scores improved more in the combination treatment group compared with the sulfasalazine alone group. At week 56, these differences were not statistically different. Moreover, in the first 28 weeks, there was a significant benefit of the combination treatment in terms of QOL measurements. In addition, the area under the curve calculation of the utility scores showed a significantly better gain of 0.06 QALY with combination treatment, as assessed by rating scale. Altogether, this investigation shows that combined treatment involving prednisolone, methotrexate and sulfasalazine is more effective, with a tendency toward lower costs than sulfasalazine alone.

Nevertheless, this combination therapy has not widely been adopted, despite the fact that persistently lower yearly rates of radiological damage progression were observed at least 4 years after the trial ended in the initial combination group.[155]

5.1.3 DMARDs and Biologic Agents

Choi et al.[156] assessed the cost effectiveness of six treatment options in methotrexate-resistant patients with RA over a 6-month period. The treatment options included: (i) etanercept and methotrexate; (ii) etanercept monotherapy; (iii) ciclosporin and methotrexate; (iv) triple therapy consisting of sulfasalazine, hydroxychloroquine and methotrexate; (v) methotrexate monotherapy continuation; and (vi) no DMARD. Two measures of efficacy were used: (i) ACR20 response criteria; and (ii) the 'ACR70 weighted response' (ACR70WR). This weighted outcome measure was calculated by a weighted average of patients achieving an ACR20, ACR50 and ACR70 response. The ACR70 had a weight of 1, and the ACR20 and 50 had a weight of 20/70 and 50/70, respectively. The investigators based their efficacy data on three double-blind trials and one open trial,[121,157-159] and they assumed that the combination of therapies caused no more adverse events than methotrexate monotherapy and that the adverse effects associated with etanercept monotherapy were negligible.

Table IV. Annual costs (converted from 1995 Dutch guilders to $US) for treating patients with rheumatoid arthritis according to treatment group[153]

Type of cost	Cost per type of treatment ($US)	
	combination of methotrexate/ sulfasalazine/prednisolone	sulfasalazine alone
Direct[a]	4354	5771
Drug	326	181
Monitoring	839	280

a Excluding drug and monitoring costs.

Drug toxicity and ACR response were part of the decision model.[156] Total costs were taken from the societal perspective and consisted of the direct costs associated with the treatment as well as indirect costs made by the patient as a cause of the disease. The direct costs included cost of the medications, mandatory monitoring costs, costs of toxicity as a result of the therapy, and costs of surgery. The toxicity costs of methotrexate were derived from hospital charges.[160] Approximately half of the direct costs of RA were related to hospital admission, mostly for surgical procedures.[161] As there is a direct relationship between the HAQ score and total direct costs,[161] the researchers developed an exponential relationship between the HAQ score and surgical costs. A recently demonstrated relationship between the HAQ score and working capacity[162] was used to estimate the cost of lost work capacity (i.e. indirect costs). With these data and the HAQ improvements, the researchers calculated the surgical related costs for each DMARD strategy.

Incremental cost-effectiveness ratios (ICERs) were calculated as the additional cost per patient to

Table V. Costs ($US, 1999 values) per 6 months for treating methotrexate (MTX)-resistant patients with rheumatoid arthritis according to treatment group[156]

Type of cost	Cost per type of treatment ($US)					
	no DMARD	MTX	triple therapy	MTX-ciclosporin	etanercept	etanercept-MTX
Total[a]	12 329	12 339	11 547	11 461	11 067	11 012
Direct[a]	1633	1793	1526	1440	1728	1310
Indirect	10 689	10 544	10 019	10 019	9852	9707
Drug	0	672	1078	2418	6600	7272
Monitoring	513	799	867	901	0	799

a Excluding drug and monitoring costs.

DMARD = disease-modifying antirheumatic drug.

achieve ACR20 or ACR70WR improvement.[156] These costs were compared with the next least expensive option to determine which one was more cost effective.

During a 6-month period, the total costs, including drug and monitoring costs, of methotrexate monotherapy continuation, ciclosporin and methotrexate combined therapy, and etanercept monotherapy were higher than no DMARD (table V). However, they were either less efficacious or had a higher ICER than the next option).[156] In other words, these strategies were not cost effective.

In Choi et al.'s[156] separate reference analysis, methotrexate for methotrexate-naive patients costs $US1100 per ACR20 outcome and $US1500 per ACR70WR outcome compared with no second-line agent (1999 values).[156] In comparison with this analysis, in the US, triple therapy costs 1.3 and 2.1 times more per patient with ACR20 and ACR70WR outcomes, respectively.[156] The most effective strategy, i.e. the combination of etanercept and methotrexate costs 38 and 23 times more per patient with ACR20 and ACR70W outcome, respectively, than methotrexate alone.[156] Whether this is cost effective depends on the acceptability of costs per ACR20 or ACR70WR outcome, $US42 600 and $US34 800 (1999 values), respectively (i.e. whether or not these costs over a 6-month period are considered acceptable, if the patient considers that the costs are too high, then this is not cost effective). Sensitivity analyses revealed that the costs of etanercept monotherapy should be reduced by >70% to cost less and be more efficacious than triple therapy.[156]

Choi et al.[148] published a similar analysis comparing five monotherapies for methotrexate naive RA patients: (i) etanercept; (ii) leflunomide; (iii) methotrexate; (iv) sulfasalazine; and (v) no DMARD (table VI). Methotrexate and sulfasalazine were found to be more cost saving than no DMARD therapy. Sulfasalazine, in comparison with methotrexate, has an ICER of $US11 500 per ACR20 response. However, when using the ACR70WR, sulfasalazine costs more and is less efficacious than methotrexate. Similarly, leflunomide also cost more and was less efficacious than methotrexate. When methotrexate and sulfasalazine are contraindicated, the incremental ratio of leflunomide, compared with no DMARD, was $US200 per ACR20 and $US300 per ACR70WR response (1999 values).

Etanercept, the most effective option has an ICER of $US41 900 per ACR20 response and $US40 800 per ACR70WR response when compared with sulfasalazine and methotrexate, respectively (1999 values).[148] This means that achieving an ACR20 response costs $US40 800 more than sulfasalazine.

Sensitivity analyses showed that a substantial reduction of leflunomide costs is necessary before leflunomide becomes the preferred option over

methotrexate.[148] Sensitivity analyses also showed that the relative cost effectiveness between sulfasalazine and methotrexate cannot be assessed conclusively, and that, therefore, sulfasalazine could also be cost effective. When the proportion of patients achieving an ACR outcome with methotrexate reaches similar proportions to that of etanercept,[122] the ICER increases to $US258 000 per ACR20 response and $US193 900 per ACR70WR response (1999 values).

5.2 Biologic Agents

A US study (published as an abstract) compared the cost efficacy of etanercept, infliximab, adalimumab and anakinra, given as monotherapy or in combination with methotrexate.[163] The assumptions for their model were based on an expert panel of rheumatologists and pharmacoeconomists, and considered only direct costs. The registered dosages for each drug were used in the study; the dose of methotrexate, applied in the combination therapies, was 15 mg/week. The ACR20 response was used as the primary outcome measure. The researchers found that the most efficacious treatment was etanercept, followed by adalimumab, anakinra and infliximab. Given as monotherapy, the costs for the four drugs ranged from $US29 654 (etanercept 25mg biweekly) to $US40 628 (infliximab 3 mg/kg every 8 weeks) per patient achieving the ACR20 response. Given in combination therapy with methotrexate, the costs ranged from $US25 478 (etanercept 25mg biweekly/methotrexate) to $US40 628 (infliximab 3 mg/kg every 8 weeks/methotrexate) per patient achieving the ACR20 response (year of values not stated).

Four cost-effectiveness papers were recently presented at the ACR meeting held in Orlando, FL, USA (24–28 October 2003).[164-167] Unfortunately, these studies also only considered direct costs. Three indicated that etanercept was the most cost-effective option[164-166] and one found that adalimumab was the optimal strategy in terms of cost effectiveness.[167]

Clearly, full reports of these five abstracts are required for more valid and reliable conclusions to be drawn. Moreover, prospective trials with a contemporary economic evaluation with explicit QOL assessments as well as the determination of the indirect costs are also needed to determine the cost effectiveness of these treatments.

5.2.1 Infliximab versus Methotrexate

Recently, three cost-effectiveness investigations with infliximab have been published.[168-170] Two analyses[168,169] used Markov models and were based on the clinical trial in 428 patients comparing the combination of infliximab and methotrexate with methotrexate alone (ATTRACT [Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy]).[108] The other trial compared etanercept with infliximab.[170]

Table VI. Costs ($US, 1999 values) per 6 months for treating methotrexate (MTX)-naive patients with rheumatoid arthritis according to treatment group[148]

Type of cost	Cost per type of treatment ($US)				
	no DMARD	MTX	sulfasalazine	leflunomide	etanercept
Total[a]	10 866	9623	10 812	9883	9565
Direct[a]	1127	1009	1673	1269	1212
Indirect	9712	8643	9112	8643	8324
Drug	0	504	109	1469	6600
Monitoring	513	799	106	76	0

a Excluding drug and monitoring costs.

DMARD = disease-modifying antirheumatic drug.

In the Swedish/UK investigation,[168] the Markov model was used to define seven disease states based on functional disability assessed with the HAQ. The disease progression in this model was based on changes in annual HAQ scores found in two cohort studies in Sweden and the UK[167,171] The QALY[168] was used as the outcome measure and utility was measured by interview-based techniques. Direct and indirect costs were derived from the two cohort investigations[167,171] and the infliximab costs were derived from the official list price. Direct costs included costs of hospitalisations, surgery, visits to healthcare professionals, and medication costs. Indirect costs included costs as a result of an inability to work.

In the basic Markov model, the clinical trial data were used for the first year.[108] Cohort data from two cohort studies[167,171] in Sweden and the UK were used to simulate a 10-year follow-up.[172] For the second treatment year, it was assumed that treatment stopped after 1 or 2 years when no further clinical data were available. The alternative Markov model (sensitivity analysis) incorporated a loss of treatment effect in the year after stopping, which appears to be a more realistic approach as the basic Markov model assumes that treatment effect is maintained after the treatment is stopped. For this latter model,[168] infliximab decreased the risk for progress into a more severe state of RA by 56% and the chance to improve to a better state was enhanced by a factor 3.5.

For the basic model,[168] including all costs, the additional costs for infliximab treatment were €864 in Sweden and €10 387 in the UK. Annual costs of infliximab were €7720 in Sweden and €12 284 in the UK. Hence, the use of infliximab reduced the total costs by €6853 and €1897 in Sweden and the UK, respectively. The QALY gain was 0.248 in Sweden and 0.298 in the UK and the costs per QALY gained were €3440 and €34 800, respectively. For 2 years of infliximab treatment, these costs increased to €16 000 per QALY gained in Sweden and €48 200 per QALY gained in the UK (year of values not clearly stated). For the alternative model,[168] when adjusted for treatment loss at discontinuation, the total costs per QALY gained were cost saving in Sweden and €29 700 ($US27 301 [2001 values]) in the UK (table VII). The marked difference between Sweden and the UK is predominantly caused by differences in indirect costs.

Altogether, this analysis shows that infliximab treatment will reduce both direct and indirect costs.[168] The costs per QALY gained appear acceptable as other commonly used medical therapies have cost-effectiveness ratios below $US50 000–$US100 000 per QALY (2001 values).[173]

Table VII. Costs (converted to $US, 2001 values) for 1-year infliximab treatment, adjusted for treatment effect lost at discontinuing therapy[168]

Type of cost	Cost per type of treatment ($US)		Incremental cost ($US)	Incremental cost per QALY ($US)
	combination of infliximab/MTX	MTX alone	difference between infliximab/MTX and MTX alone	difference between infliximab/MTX and MTX alone
Sweden				
Direct costs	25 371	19 901	5470	23 680
All costs	114 254	117 163	−2909	Cost saving
UK				
Direct costs	30 751	20 018	10 733	41 440
All costs	66 964	59 893	7071	27 301

MTX = methotrexate; **QALY** = quality-adjusted life year.

A similar model was used for the American study[169] and consisted of 21 health states (death being the 21st health state) based on the combination of five treatment strategies (i.e. a combination of methotrexate and infliximab, methotrexate monotherapy, DMARD monotherapy, a combination of methotrexate and another DMARD, a combination of corticosteroid and NSAIDs), four disability levels assessed by the HAQ (0 = no impairment; 0.1–1 = mild impairment; 1.1–2 = moderate impairment; and 2.1–3 = advanced impairment), as well as death. The Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) database, trial results and published data were used to determine direct and indirect costs, QOL and disability estimates. For the first year, the treatments were the same as in the ATTRACT investigation ([i] a combination of infliximab and methotrexate; and [ii] methotrexate monotherapy).[108] Thereafter, the disability score and current treatment determined whether or not a new treatment was given. At 54 weeks, it was assumed that infliximab would be discontinued.

This investigation revealed that 54 weeks of combined infliximab and methotrexate treatment decreased the probability of having severe disease from 23% to 11% at 54 weeks, leading, on a life-time basis, to a 1.7-month increase in life expectancy and a 4-month QALY gain compared with methotrexate alone.[169] In this case, first-year costs with infliximab plus methotrexate were >$US10 500 and life-time costs were >$US9000 with methotrexate alone. The cost-effectiveness ratio for combination treatment was $US26 800 per QALY gained. Sensitivity analysis showed that a combination of infliximab and methotrexate was more cost effective in patients with a lower weight, in patients who had a higher quality of life with the combination treatment, or in patients with more progressive disease.

Taken together, the results of these two investigations[168,169] appear to be generally similar. Although there are inherent shortcomings as a result of the study design as the data were extrapolated from a 1-year study, the omission of radiological data (and its effects on disability) and the omission of the increased risk of infections in the models, these two studies establish an insight into the elements of cost effectiveness of infliximab. Additional (long-term) follow-up investigations are required to confirm the finding.

5.2.2 Infliximab versus Etanercept

Another study compared the total costs associated with two different TNF antagonists, infliximab (administered in combination with methotrexate) and etanercept.[170] The cost evaluation of this Dutch investigation included direct medical and non-medical costs and indirect costs (1999 values). This analysis revealed that the yearly drug costs were similar for infliximab and etanercept, i.e. $US12 610 for infliximab and $US12 534 for etanercept. However, other medical costs were substantially higher for infliximab compared with etanercept, $US5048 and $US107, respectively. This difference was mainly as a result of the outpatient setting required for infliximab and the concomitant methotrexate use.

This study[170] was based on several assumptions, which can potentially be disputed. For instance, the study assumed that a medical specialist was required to administer infliximab; however, it may be more common for a nurse to insert a needle for intravenous infusion, rather than a doctor (for instance). The time required for the preparation of infliximab that was used as an estimation in the study may also be too high as the times used for this study were interview based. Hence, reliability can be questioned. Moreover, in clinical practice it is likely that the administration of the drug is carried out simultaneously for several patients, which is cost saving. Moreover, the time to reach efficacy is much shorter for infliximab than for etanercept, which could have

a significant positive impact on quality of life. Finally, clinical practice shows that a substantial number of patients prefer one infusion in 8 weeks rather than twice weekly subcutaneous injections. On the other hand, a recent prospective study indicated that 57% of the patients treated with infliximab require an increased dosage or a shortened interval duration to maintain symptomatic control, which leads to higher drug costs.[174] Altogether, these shortcomings should be first assessed adequately to make justified statements of the comparative cost effectiveness of these two drugs.

Another investigation compared the dosages used in a clinical environment of etanercept and infliximab in patients with RA.[175] The primary outcome measure was the ACR50 response criteria. The calculated costs per patient achieving the ACR50 response criteria was $US36 293 and $US54 435 for etanercept and infliximab, respectively (year of values not clearly stated).

The available data suggest that etanercept may be more cost effective than infliximab; however, for more substantial conclusions to be drawn further studies are required, particularly those assessing incremental cost ratios per QALY.

5.2.3 Adalimumab

An interesting cost-saving option could be dose titration of adalimumab on the basis of a disease activity score (DAS), as that investigated in the DAS28 study.[176] This limited open-label study in 21 patients with RA indicated that dose reduction was possible in 15 patients with a total adalimumab-dose reduction by 67%. Given that TNF antagonists are costly, the option of dose titration may reduce costs and requires more extensive investigations.

5.2.4 Anakinra

Complete cost-effectiveness studies of anakinra are not yet available. An interesting abstract indicated that, after 6 months, patients treated with anakinra 150 mg/day had gained more productivity days than those treated with placebo.[177] Moreover, this improvement occurred rapidly. The gain in productivity days for patients treated with anakinra 30 or 70 mg/day was similar to that of placebo. It remains to be established whether or not the recommended dose of anakinra 100 mg/day has a favourable effect on the productivity.

Guh et al.[178] investigated the direct and indirect costs as well as QOL assessments of three treatment strategies: (i) low-dose (1 mg/kg) anakinra plus methotrexate; (ii) high-dose (2 mg/kg) anakinra plus methotrexate; and (iii) methotrexate alone. The incremental cost per additional patient achieving the ACR20 response was $Can51 982 and $Can79 267 for the low and high dose anakinra, respectively, versus methotrexate alone. The incremental costs per QALY were $Can106 356 and $Can95 774, for the low and high dose anakinra respectively, versus methotrexate alone. These high costs reflect the limited superior efficacy/safety ratio of anakinra over methotrexate (2003 values).

6. Conclusions

6.1 Efficacy

Numerous studies have demonstrated the long-term efficacy of methotrexate and there are indications that this drug might lead to a survival benefit by decreasing cardiovascular morbidity.[179] While sulfasalazine has been shown to be effective in treating RA, the drug survival rate is significantly less than that of methotrexate. Moreover, the evidence that sulfasalazine reduces radiological damage is less convincing. There is some evidence that leflunomide has a similar efficacy to that of methotrexate, in particular that leflunomide has a similar halting effect on (progression of) radiological damage.

The literature is contradictory whether or not combination DMARD therapies with methotrexate, sulfasalazine and hydroxychloroquine, or methotre-

xate and sulfasalazine, are more effective than the DMARDs alone. Combination therapies with methotrexate plus sulfasalazine (hydroxychloroquine) and prednisolone seem to be superior to sulfasalazine alone. The efficacy of combination therapy leflunomide plus methotrexate has been shown in patients with a partial response to methotrexate.

TNFα antagonists have a rapid onset of action, that is, within 2 weeks, compared with traditional DMARDs. Indeed, the mode of action of infliximab and adalimumab is faster than that of etanercept. TNF antagonists (with or without methotrexate) have a superior efficacy compared with methotrexate, in patients with established disease as well as early disease, and appear to inhibit radiological damage to a greater extent than methotrexate. However, the observed radiological differences are small and their (long-term) relevance remains to be established.

The IL-1 receptor antagonist anakinra appears to be less efficacious (according to ACR responses) than the TNFα antagonists. However, a favourable effect on radiological deterioration remains to be shown with the registered dose (100mg once daily) of anakinra.

6.2 Tolerability

The adverse effect profiles of methotrexate, sulfasalazine and leflunomide, are broadly similar. Typical adverse effects associated with methotrexate include alopecia and stomatitis, and adverse events typically associated with sulfasalazine include gastrointestinal and haematological adverse effects. Leflunomide is associated with gastrointestinal adverse effects and allergic reactions. The adverse effects of leflunomide persist for longer than other DMARDs because of the long elimination half-life of this drug.

Adverse effects of the biologic agents include an increased incidence of common and opportunistic infections. However, thus far anakinra has not been associated with an enhanced rate of opportunistic infections. Occasional adverse effects for infliximab include possible aggravation of heart failure and (aggravation of) demyelinating disease. Etanercept has also been occasionally associated with demyelinating disease. Anakinra has been associated with injection site reactions and neutropenia.

6.3 Cost Effectiveness

Cost-effectiveness analyses revealed that the total costs for leflunomide were significantly higher than those of methotrexate. Studies where costs per QALY were determined showed that for leflunomide the costs per QALY ranged between $US54 000 and $US72 000, and for the combination infliximab plus methotrexate the costs per QALY gained was $US27 000. In another investigation, the total direct costs of the combination methotrexate, sulfasalazine and prednisone were similar to that of sulfasalazine alone.

Interesting modeling studies showed that the costs per ACR20 responder varied between $US25 000 and $US65 000 per year for the biologic agents. In another study, the costs per patient achieving the ACR50 response criteria were $US36 293 and $US54 435 for etanercept and infliximab, respectively.

The incremental cost per QALY gained of anakinra plus methotrexate versus methotrexate alone ranged between $US96 000 and $US106 000 per QALY, thereby demonstrating the limited advantage of anakinra over methotrexate.

Restricting ourselves to direct costs only reveals that the costs of biologic agents are significantly higher in comparison with DMARDs. The indirect costs from disability as a result of RA are substantial and the inclusion of indirect costs in pharmacoeconomic analyses is important. However, biologic agents may have beneficial effects on the medium or long-term usage of the health system by reducing

functional decline with a concomitant lowering of indirect costs, for example a lower rate of hospital visits or orthopaedic surgical admissions, ultimately leading to lower costs compared with DMARDs. Unfortunately, these data are not yet available as studies are yet to be performed in this area. Moreover, the lower functional decline that may be associated with biologic agents will lead to a less frequent use of disability insurance because of a decrease in the loss of productivity. Hence, it was suggested that health and disability insurance should be integrated, as now costs for health insurance lead to profit for disability insurance.[3]

7. Discussion and Recommendations

The treatment of RA has made substantial improvements in the last few decades. The pyramid therapy has changed to the application of DMARDs early in the disease, aiming at arresting or inhibiting joint damage in view of the considerable radiological damage that may already exist at this stage. The other major advance in the pharmacological treatment of RA was the development of biologic agents, which presently appear to be efficacious in RA.

The most effective DMARD today appears to be methotrexate, followed by leflunomide and sulfasalazine. Leflunomide is more effective than sulfasalazine, but this advantage might be offset by its adverse effect profile. Several DMARD combination therapies have proven to be effective and well tolerated, showing benefits over mono-DMARD therapy, although it is unclear when they should be used and, thus, these strategies have not yet been widely adopted. Moreover, comparative trials with biologic therapies are lacking. Therefore, we conducted a single-blind multicentre investigation in 508 patients with early RA (<2 years) comparing four groups: (i) sequential monotherapy with methotrexate, sulfasalazine and leflunomide; (ii) step-up therapy with methotrexate, the addition of sulfasalazine, followed by hydroxychloroquine; (iii) step-down therapy from the initial combination methotrexate, sulfasalazine and prednisolone 60mg (tapered to 7.5 mg/day); and (iv) infliximab plus methotrexate.[180] The preliminary results of this study indicated that after 1 years' treatment, both the initial combination therapy and infliximab plus methotrexate resulted in a better and faster clinical response as well as less radiological damage than the sequential monotherapy or step-up therapy. HAQ scores decreased by 0.7 points in the first two treatment groups (i and ii) and 0.9 in the other two groups (iii and iv) [p = 0.040]. There were no significant differences in the drop-out rates or the number of serious adverse events between the four groups.

Presently, biologic agents are reserved for those patients who have not responded to 'conventional' DMARD therapy, with the exception of etanercept, which has been registered in the US for use DMARD-naive patients with RA. The three presently available TNFα antagonists (infliximab, etanercept, adalimumab) appear to have a similar efficacy between them, although direct comparative investigations are lacking. There is indirect evidence that the efficacy of anakinra (an IL-1 antagonist) is lower than that of the TNFα antagonists. Comparative trials in patients with established RA have shown that biologic agents with or without methotrexate have a higher clinical efficacy and a faster onset of activity than methotrexate monotherapy. Studies in patients with early RA showed that biologic agents with or without methotrexate have a similar or more favourable efficacy than methotrexate alone, although the absolute differences were small. Moreover, there was a tendency for a slower or more arrested radiological damage with the biologic agents compared with methotrexate.

There remain several areas of uncertainty despite these promising results of the biologic agents. These are discussed as follows.

1. It remains to be proven whether or not these limited efficacy advantages of the biologics over methotrexate, particularly in early RA, will be of clinical relevance in the long term. Moreover, most of these trials compared biologic agents with methotrexate in doses up to 20 mg/week. Nowadays, methotrexate 25 mg/week is more commonly administered, which could eventually lead to a smaller efficacy advantage for the biologics compared with methotrexate;

2. It is yet to be determined whether or not the efficacy advantages will be offset by long-term adverse effects (i.e. increased risk of severe and/or opportunistic infections and other serious, but infrequent, adverse effects such as aggravation of heart failure patients, induction of demyelinating disease, or development of malignancies). The adverse effect profile of the TNFα agents tends to differ between the three agents; more post-marketing data are mandatory before distinction between the agents, if any, can be made.[181] To date, sound safety data beyond 5 years of treatment are lacking. Moreover, these data will reveal whether or not the observed differences in adverse effect profiles of the biologics are indeed true and of clinical relevance. It should be noted that, to date, no data exist to indicate that anakinra increases the risk of opportunistic infections in RA.

3. Cost considerations influence the use of biologic agents, because they are relatively expensive, with yearly drug costs of >$US20 000. Hence, there should be a careful weighing up of the total costs of the various treatment strategies and whether they ultimately lead to prevention of long-term disability (which may mean they are cost saving). However, real-time longitudinal data on life-time costs of RA are not available. An interesting approach was an analytical model in which population-based and economic data were used. The investigators calculated median incremental (direct and indirect) costs, over the first 25 years of RA, ranging from $US61 000 to $US122 000 (1995 values) with an upper limit of $US300 000.[182,183] Hence, biologic and/or DMARD treatment may be cost saving if some of these costs could be eliminated; in particular, indirect costs should be lowered.

There have been several economic cost-effective evaluations of DMARDs and biologics in RA; however, they were either partial economic evaluations, modeling studies or supported by pharmaceutical companies. Adequate objective economic long-term evaluations, incorporating prospective efficacy and safety data are lacking. It will take several years before the results of these studies will be available. In the meantime, treatment decisions will be based on the balance of direct and indirect costs, which can be reliably assessed but may vary substantially between and within nations, and indirect future costs are expected to be lowered by the combination of DMARDs and biologic agents. Such an assessment is even more difficult as clinical experience reveals that up to 40% of patients do not or only partially respond to biologic therapy.[184] Therefore, one of the challenges is to identify those patients who are likely to respond to these therapies or those who require adapted dose regimens of TNFα antagonists.[185]

Practical guidelines are difficult to provide in view of the different international, national and local guidelines, available facilities and resources, and variable costs of medications. The common practice in hospitals in The Netherlands for typical postmenopausal women with RA, is to start with methotrexate followed by leflunomide or sulfasalazine in case of inefficacy/intolerability. Then, in case of ineffficacy or intolerability of two DMARDs, after a few months we administer a TNFα antagonist. There could be a slight preference for adalimumab and etanercept, rather than infliximab, in view of their lower costs and ease of administration. On the other hand, a survey in The Netherlands indicated a preference for (continua-

tion) of intravenous administration if the patient could choose between infliximab and etanercept.[186] When patients do not respond to, or are intolerant of, treatment with a TNFα antagonist then another TNFα antagonist is administered (as some patients who do not respond to one TNFα antagonist might respond to another anti-TNFα agent[187,188]), or anakinra is administered. Anakinra may also be the preferred treatment if an increased risk for an opportunistic infection cannot be excluded or in patients with heart failure. Ongoing investigations will determine the precise place of combination treatment(s).

In summary, biologic agents have induced a tremendous change in the treatment of RA; however, debates regarding their application will remain until satisfactory long-term efficacy and safety data as well as objective and prospective economic analyses are available. These analyses will also reveal whether or not there is a long-term advantage of biologic agents over conventional DMARDs.

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