Safety of anakinra, a recombinant interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis and comparison to anti-TNF- agents

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Clin Exp Rheumatol 2002; 20 (Suppl. 27): S35-S41.

Key words: Biological response modifiers, anakinra, etanercept, infliximab.

ABSTRACT

Anakinra is a recombinant human interleukin-1 receptor antagonist (IL-1ra) recently approved by the FDA as a new therapy for patients with rheumatoid arthritis. Four clinical trials have been completed which have demonstrated that anakinra is an effective anti-rheumatic therapy either used alone or in combination with methotrexate. The most frequent adverse events reported in the clinical trials are injection-site reactions which are generally mild to moderate and rapidly resolve. A large, prospective safety study which allowed a wide-variety of co-morbid conditions and concomitant medications demonstrated that anakinra therapy is a well-tolerated treatment for rheumatoid arthritis in the patient population seen by the practicing rheumatologist. Unlike therapies designed to affect TNF- , there have not yet been reports of the development of tuberculosis or other fungal infections, demyliniating syndromes or worsening of congestive heart failure.

The safety profile of etanercept and infliximab were similar to that of anakinra in the phase I – phase III clinical trials. Unlike anakinra, these medications were not studied in the usual rheumatoid arthritis population which includes a number of patients with a wide variety of co-morbid disease and utilizing a number of concomitant anti-rheumatic medications. Post approval, several safety concerns, including patients at risk for serious infection and the emergence of latent tuberculosis and other opportunistic infections have emerged with the use of anti TNF therapy.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder which often causes progressive destruction of peripheral joints leading to significant deformity and disability (1,2). In the vast majority of patients with RA, there is a significantly increased incidence of comorbid diseases and increased mortality (3) with a decreased average life expectancy by 3 to 18 years, depending upon disease severity (4). Although the most rapid progression of disease occurs during the first five years (5) of illness, it is clear that there is progressive deformity and disability over the entire lifespan of most patients. Because of the realization that without the aggressive institution of medications targeted to at least slowing, if not preventing, the inflammation of RA (and therefore the subsequent deformities and disabilities associated with progressive disease) in the past decade, rheumatologists have used disease modifying anti-rheumatic drugs (DMARDS) earlier and in combination in an effort to obtain more effective control of clinical symptoms and to retard joint destruction in an effort to improve long-term outcomes (6-9). Traditional DMARDs are frequently associated with significant toxicity or diminishing efficacy over time which, with the possible exception of methotrexate (MTX), does not allow many patients to obtain maximally effective disease management over the many years that the disease is active (10-12). The outgrowth of this thinking has been the realization of the need for new and novel treatments for patients with RA that are safer and more effective than traditional DMARDs and that can be significantly more effective in reducing inflammation and disease progression whether used alone or in combination with existing therapies for long-term treatment.

Within the past 4 years, several biologic response modifiers (BRMs) which specifically target IL 1 or TNF have been introduced into clinical practice. In phase II and III clinical studies,

these biologics have been shown to be very effective in controlling clinical symptoms and in retarding x-ray progression in patients with RA(13-20). BRMs appear to have different safety profiles from traditional DMARDs as well as from each other. Although there has not yet been enough long-term safety data with BRMs, it is possible that, if their long-term safety profile is relatively benign, this difference in safety and tolerability may allow the continuance of these medications over the many years of active disease, which may well significantly reduce the deformities, disabilities, co-morbidities and mortality that patients have had to endure over the past centuries. The purpose of this manuscript is to describe the significant adverse events that have been described with each of the presently approved BRMs (anakinra, etanercept and infliximab) and compare the incidence and the differences in types of adverse events that occur with all three agents.

Comparative safety analysis

Whether analyzing or comparing safety data of various medications, it is of paramount importance to understand the primary source and validity of the safety reports. The safety data collected in phase I clinical trials is generally designed to show only the development of common toxicities produced by the agent being tested. There are usually only a few individuals who take active medication and they may well be healthy "volunteers" rather than patients with the disease under study. These safety studies show, because of the small numbers of subjects enrolled, only very common toxicities of the agent being utilized. Similarly, phase II and III clinical efficacy studies, although utilizing patients with the disease in question, are unlikely to demonstrate the development of significant adverse events that occur only infrequently in association with the medication. This occurs because these studies are not statistically powered to show the occurrence of rare, but significant, events and the fact that patients with significant co-morbidities or those taking multiple medications are almost always excluded from these trials (21). Very large phase III and phase IV safety studies may well be powered to show small differences that may well be clinically significant (21). Long term open-label safety studies of patients previously treated in a double-blind, placebo-controlled trial may give some useful long term safety information but are flawed by the fact that only patients who initially had a response to the medication and who did not have a significant adverse event (AE) are included. They are useful, however, for detecting adverse events that will only become evident after a significant time on drug.

To detect rare but important adverse events with medications generally requires the treatment of large numbers of patients with the disease in question and who also have the usual co-morbidities and are on usual concomitant medications that may increase the risk of developing such adverse events (21). The three most common types of such studies that are performed are: (1) post-marketing sponsor (pharmaceutical) directed safety surveillance studies in which the sponsor makes an intense effort to contact virtually all the patients on the medication once it is released and follow them prospectively for the development of significant adverse events; (2) spontaneous reports to the sponsor or a regulatory authority such as the Federal Drug Administration from patients or physicians who suspect that an adverse event has occurred from the medication; and (3) post-marketing pharmacovigiliance studies in which prospective safety data of large numbers of patients is collected in a systematic manner. Each of these methods has significant advantages and disadvantages. All, however, may be far superior to phase I – III clinical efficacy studies and phase III and phase IV clinical safety studies which either are not adequately powered to detect significant differences or which may not include the patients at true risk of developing the AE.

What is of most interest in comparing relative safety of medications,however, is to be sure that the source of the data is reliable and consistent between the two studies. Thus, it would clearly be inappropriate to compare the safety profile of drug X which is studied in 10 healthy volunteers for one week to drug Y which is prospectively studied for 5 years in 10,000 patients with the disease in question, who have the usual comorbid conditions and are taking the usual concomitant medications employed in treatment of the disease in question.

Thus, one can safely compare safety of different medications, even if not compared in the same study, as long as the patient population is exactly similar and if the safety parameters are reported in a similar manner, the source of the safety data is similar (e.g. 1 year post-marketing analysis of safety in all patients with rheumatoid arthritis with similar concomitant medication) and the data is reported in a comparable manner (e.g. events/patient/year). To compare efficacy accurately, however, both medications must be used in the same study with similar patient characteristics, concomitant medications, co-morbid disease and analyzed in the same manner statistically.

Safety of traditional DMARDs

Gold

Parenteral organic gold compounds, which were originally developed to treat infectious disease, have been used successfully since the 1920's for the treatment of rheumatoid arthritis (22). With respect to efficacy, there are studies which show that the comparison of weekly administration of 50 mg of parenteral gold with weekly administration of 15 mg of MTX showed a higher proportion of patients reaching remission with gold but also increased toxicity with gold (23). There have not been studies which have compared the comparative safety and efficacy of gold treatment with the higher dose of 20-25 mg per week of MTX commonly employed in the 21st century. Adverse reactions including mucocutaneous reactions, proteinuria and cytopenias have limited gold's use.

Sulfasalazine

Sulfasalazine has numerous toxicities, which limits its clinical usefulness (24) including GI side effects (including

Table I. Baseline demographics and disease state.

	Mono 1 N = 472	Mono 2 N = 141	MTX 1 N = 419	MTX 2 N = 501	Safety N = 1399
Female %	75	77	78	77	75
White %	99	100	89	87	89
Age (yr)	53	52	53	56	55
Weight (Kg)	70	70	79	81	77
Years with RA	4	3.5	7.4	10.8	10.3
Tender joints (0-68)	34	33	25	26	23
Swollen joints (0-66)	26	24	18	20	19
HAQ (0-3)	1.57	1.64	1.4	1.34	1.41
CRP (mgldl)	4.14	3.17	1.91	2.63	2.67
ESR (mm/hr)	50	43	37	42	N/A

transaminitis), rash,neutropenia, aplastic anemia, agranulocytosis, hemolysis, yellowish discoloration of skin, urine and contact lenses as well as reversible infertility in men. Sulfasalazine is, however, an effective medication which can be used beneficial clinically for years if toxicity does not develop.

Methotrexate

Prospective long-term studies have shown that MTX is better tolerated and more efficacious than other traditional DMARDs and that a far higher percentage of patients remain on MTX for a longer period of time when compared to these DMARDs (25-27). Side effects include stomatitis, GI intolerance, and bone marrow suppression (all responsive to folic acid supplementation), idiosyncratic allergic-like lung injury and liver damage (28,29). It is an abortifacient and causes birth defects. Conception should be avoided on this medication and both males and females should employ appropriate contraceptive measures.

Leflunomide

Leflunomide is an anti-proliferative isoxazole compound. A placebo controlled trial compared leflunomide, MTX and placebo for 52 weeks (30). Two trials explored the combination of leflunomide with MTX (31, 32). A significant number of patients in both trials had elevated transaminases. Common side effects of leflunomide, seen in all three trials, are diarrhea, dyspepsia, abdominal pain, hypertension, rash, reversible alopecia and headaches.

Anakinra

Demographics of placebo controlled trials

There have been five placebo controlled trials of anakinra involving a total of 2,932 patients. Two of the trials involved the use of anakinra as monotherapy versus placebo; two trials explored anakinra in combination with methotrexate; the last trial was a large, placebo controlled trial of 100 mg per day of anakinra versus placebo in a target RA patient population that included a wide array of comorbid conditions as well as concomitant medications (33-38). The baseline characteristics of these patients are shown in Table I and concomitant medications in Table II. Only the large, prospective safety study allowed patients to take a wide variety of concomitant medications and also had a variety of co-morbid diseases. The patients in all 5 studies were predominately Caucasian, female, mean age in the 50's and had active disease. The patients in the monotherapy studies had a shorter duration of RA compared to the patients treated in combination with methotrexate or in the wide-ranging safety study. In all studies patients could be treated with stable doses of non-steroidal anti-inflammatory drugs or steroids (≤10 mg/ day). In the monotherapy studies, patients could not currently use any DMARDs or other biologics. In the combination studies, all patients had to be on methotrexate but no other concurrent DMARDs or biologics. In the large safety studies, patients were allowed to be on any combination of NSAIDs, steroids and DMARDs but no other biologics. Completion rates in the five studies ranged from 73 – 88%. There have been patients who have been treated with anakinra for over 6 years.

Safety results in placebo controlled trials

There were no significant differences between placebo and any dose of anakinra up to 100 mg per day with respect to the development of adverse events (AE) (85-92%), serious AE (6.5 – 8.4%), death (0.1 – 0.3%) or withdrawal due to AE (9.5 – 13.6%). There was a slightly higher rate of occurrence in all these categories in doses of anakinra greater than 100 mg/day, most of which were due to injection site reactions (ISR). ISR was the most common cause for withdrawal with anakinra occurring in 1.3% of placebo patients, 7.3% of patients taking 100 mg per day and 7.1% in patients taking more than 100 mg per day. The most common reason for withdrawal in the placebo group and low dose anakinra was, not unexpectedly, worsening of their rheumatoid arthritis which occurred in 6.2% of the placebo group and 4.8% of anakinra < 100 mg per day.

Patients were required to self-administer daily subcutaneous injections of anakinra. Although there was concern about whether patients would be com-

Table II. Baseline RA medications.

%	Mono 1	Mono 2	MTX 1	MTX 2	Safety
Steroid	42	44	64	53	58
NSAID	84	86	69	76	87
MTX alone	0	0	100	100	31.1
DMARD (no MTX)	0	0	0	0	25
MTX + DMARD	0	0	0	0	22

Table III. Serious infectious episodes.

	Placebo	Anakinra (100 mg)	(> 100 mg)
Number (%)	759	1367	196
Any	5 (0.7)	25 (1.8)	4 (2.0)
Pneumonia	0 (0.0)	12 (0.9)	0 (0.0)
Other Respiratory	2 (0.3)	3 (0.2)	1 (0.5)
Cellulitis or Abscess	1 (0.1)	7 (0.5)	1 (0.5)
Bursitis	0 (0.0)	1 (0.1)	1 (0.5)
Osteomyelitis	0 (0.0)	2 (0.1)	0 (0.0)
Pelvic	0 (0.0)	0 (0.0)	1 (0.5)
Herpes Zoster	0 (0.0)	0 (0.0)	1 (0.5)
UTI	1 (0.1)	0 (0.0)	1 (0.5)
GI	1 (0.1)	3 (0.2)	0 (0.0)

pliant with this regimen, it was found that patients missed very few injections with approximately half the patients missing no injections and another 35% missing less than 7 injections in a 6 month period. 27% of placebo patients developed "ISR" while 71% of patients in the 100 mg per day group developed such reactions (36). ISR were generally mild to moderate in intensity and were characterized by erythema, pruitus, rash, pain or ecchymosis. ISR occurred early and if they did not develop within the first 4 weeks of therapy, they were unlikely to occur thereafter. At 100 mg per day, 95% of the ISR were mild to moderate. If an ISR did occur, almost all responded to topical applications of steroids.

Serious adverse reactions (SAE)

In clinical trials, adverse events are described in two different manners. The first is whether or not the adverse event is serious (SAE). SAE is a regulatory term that includes events which are: (1) fatal, (2), life threatening, (3) results in or prolongs hospitalization, (4) is persistent and results in significant disability or incapacity or (5) causes a congenital abnormality. The second manner is whether or not the event is mild, moderate or severe. This determination is made by the investigator, utilizing clinical perspective, irrespective of whether or not it is serious. SAE in the placebo groups were largely worsening of rheumatoid arthritis (1.6%) and arthralgia (1.6%). In the 100 mg per day group, SAE occurring in > 0.2% of patients included worsening of rheumatoid arthritis (0.7%), pneumonia (0.9%), abdominal pain (0.3%), abdominal hernia (0.2%) and dyspnea (0.3%) (39).

Table IV. Pneumonia.

Age/Sex	Pneumonia Type	Medical History	Meds	Outcome
42 F	Pneumonia	None	DMARD Steroid	Withdrawn
56 F	R Middle Lobe	COPD Asthma	DMARD	Continued
77 M	Interstitial	None	DMARD Steroid	Continued
64 M	Pneumonia	COPD Asthma	DMARD Steroid	Continued
62 M	Right Lower Lobe	CAD, CHF	None	Continued
66 M	Left Lower Lobe	Pneumonia, Asthma, CHF	DMARD Steroid	Continued
59 F	Empyema, Pleural effusion	Pneumonia Asthma	Steroid	Continued
46 M	Left Lung	Pneumonia COPD	DMARD Steroid	Withdrawn
51 F	Pneumonia	None	DMARD Steroid	Continued
62 F	Bronchopneumonia	Asthma	DMARD Steroid	Continued
72 M	Strep. Pneumonia	COPD Fibrosis	DMARD Steroid	Withdrawn
64 F	Left Lower Lobe	None	None	Withdrawn
64 F	Pneumonia, CHF	COPD, CAD	DMARD Steroid	Continued
66 F	Legionella Pneum.	None	DMARD Steroid	Withdrawn

Infections

Infectious episodes occurred at a similar rate in the placebo treated (36%) and the anakinra 100 mg per day group (40%). Serious infections occurred in 0.7% of placebo treated patients and 1.8% of anakinra 100 mg per day treated patients. Withdrawal due to serious infections occurred in 0.8 % of the placebo group and 1.2 % of the anakinra 100 mg per day group. The rate of infection in all studies did not appear to be higher than placebo or higher than what has been previously reported in this population (40).

The most common infection in the anakinra group was pneumonia as shown in Table III. Of the 14 patients who developed pneumonia in the anakinra group, 13 had a history of chronic obstructive pulmonary disease (COPD), asthma, coronary artery disease, congestive heart failure, prior pneumonia and/or were concomitantly treated with steroids or other DMARDs. There are four important points to consider with respect to the pneumonias in these studies: (1) the pneumonias were typical of patients with rheumatoid arthritis, were treated with usual antibiotics and no deaths occurred; (2) of the 14 patients who developed pneumonia, 9 continued and completed the study without further problems with pneumonia; (3) many other patients in these studies with these same risk factors did not develop pneumonia; (4) the large safety study of 1399 patients did not exclude patients on a wide variety of concomitant medications and with significant co-morbid disease. Details of these 14 patients are shown in Table IV.

Large, prospective safety study

The large, randomized, placebo controlled, wide-ranging safety study was undertaken to characterize further the safety profile of anakinra in a patient population with diverse disease activity and co-morbid conditions utilizing the approved dose of anakinra (36). The trial was designed to assess overall de-

velopment of AEs that may occur at low incidence and require a larger number of patients to permit detection. This is the first randomized, placebo controlled trial of a biologic in which a variety of co-morbid conditions (including a history of asthma, diabetes, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure or pneumonia) were allowed. The first 6 months of the study was randomized, double-blind, placebo-controlled and has been followed by an open-label phase in which patients continue in the study and are treated with anakinra for up to an additional 30 months. Patients were required only to have rheumatoid arthritis for at least 3 months with evidence of active disease defined by a minimum of 3 swollen joints and 3 tender/painful joints, or 45 minutes morning stiffness. This trial was designed to mimic the "real world" in that patients were allowed to be on NSAIDs, corticosteroids and DMARDs, either alone or in any combination, and were allowed to adjust these medications during the course of the study if clinically indicated. By design, as few patients as possible were excluded. Patients were randomized 4:1 to anakinra 100 mg per day or placebo.

A total of 1414 patients were included in the trial and 1399 patients received at least one dose of study drug or placebo. Of these 1399 patients 79.0% (1105/1399) completed 6 months of treatment: 78.4% (875/1116) receiving anakinra and 81.3% (230/283) receiving placebo. Patients were allowed a wide variety of concomitant medication. Approximately 30% received methotrexate alone, 22% were treated with MTX in addition to other DMARDs and 21% received no DMARD therapy. Almost half of patients were treated with a combination of corticosteroids and DMARDs, while 10% received no DMARDs or corticosteroids.

Adverse events and serious adverse events including infection occurred at the same rate as occurred in both monotherapy and both methotrexate combination studies. As previously shown, there was a small difference in the incidence of serious infections in the anakinra group. Virtually all of the pneumonias that have occurred in anakinra studies occurred in this study. The patients who developed pneumonia were more likely to have had a history of asthma, COPD or prior pneumonia and also more likely to be receiving steroids. The infection rate seen in these studies is consistent with previous reports in similar rheumatoid arthritis populations (40).

Other safety issues with anakinra

Unusual or opportunistic infections such as tuberculosis, histoplasmosis, listeriosis and aspergillosis, which have been observed in patients using other biologic RA therapies, were not observed in any of these studies. The short half-life of anakinra compared to etanercept and especially infliximab, may explain the lack of occurrence of some of these adverse events with anakinra (although this will not be clear until there is large post-marketing experience). The short half-life may provide more flexible control of therapy with respect to safety.

It has also been observed that the anakinra study population demonstrated a small decrease in neutrophil and platelet counts. Very few patients developed significant neutropenia. It is conjecture that the decrease of the neutrophil and platelet count reflect the anti-inflammatory effect of anakinra, but caution should be observed, and neutrophil counts followed, until this is clear.

Malignancies occurred in the anakinra patients at the same rate as would be expected in an age and sex matched control group (National Cancer Institute Surveillance Epidemiology and End Results (SEER) database). The types of malignancies were also similar to this same database.

In summary, these studies showed no difference with anakinra compared to placebo in the incidence of AEs, withdrawal due to an AE, malignancies, or death. An overall increase in the incidence of serious infection was observed with anakinra (1.8% of patients) compared with placebo (0.8%), primarily because of the large safety study which allowed patients with a wide variety of co-morbid disease and concomitant medications.

Combination of anakinra with other biologics

A 24 week safety study of the combination of an IL1-ra and an anti TNF was performed to try to determine the safety of combining biologics in patients with RA. Anakinra 1 mg/kg/day was added to etanercept 25 mg BIW in an open label study of 58 patients who had active disease in spite of taking etanercept (38). The patients were predominately female in their late 40's with mean disease duration of 12 years. In spite of taking etanercept for a mean over one year, the patients still had active disease with a mean of 26 tender and 17 swollen joints with a mean CRP of 2.2. After 24 weeks, patients did have decreases in tender and swollen joints, HAQ, ESR and CRP.

The primary outcome of the study was safety. There were no deaths and 7 serious adverse events (12.1%). Three of these events were accidental electrocution, opiate/barbiturate withdrawal and gastric ulcer with a bleed. The other 4 serious adverse events were infectious including two cases of pneumonia and two cases of cellulitis (7%). All patients recovered.

A much larger, double blind, placebo controlled trial is currently underway to examine the safety of this combination. Until the results of this study are known, it is not recommended that anakinra be combined with an anti-TNF in clinical practice.

Safety of anti-TNF agents

It has become clear, both from randomized controlled trials but, more importantly, from post-marketing surveillance studies and spontaneous reports to regulatory authorities, that different biologics may well have different safety profiles.

Etanercept

In the many clinical trials of etanercept performed in RA, the only safety concern apparent has been injection site reactions which occurred very similarly to anakinra in its clinical trial (41). Unlike, anakinra, however, there was no pre-approval, placebo, controlled, large safety study in which patients could have a wide-spectrum of co-mor-

bid diseases and be on a wide variety of anti-rheumatic therapies.

Since the approval of etanercept, there have been several safety concerns which have emerged, primarily from post-marketing reports. The true incidence and relationship to therapy with etanercept is still unclear. Four cases of patients who developed confusion and difficulty walking while on etanercept have been reported (42) out of the approximately 90,000 patients who have been treated with etanercept. The events were temporally related and resolved or diminished on discontinuation of therapy. One patient had a positive re-challenge. Such events have been reported with other inhibitors of TNF and thus this may be a class effect. It is therefore suggested that etanercept not be instituted in patients with demylinating diseases. If a patient develops neurological symptoms while on etanercept, therapy should be discontinued. Also noted has been the development of tuberculosis, pancytopenia, and aplastic anemia, A true relationship to etanercept has not been established, however (43).

In those patients predisposed to infection, such as diabetics and those with chronic infections such as chronic urinary tract infections,etanercept therapy is relatively contraindicated and a comprehensive risk/benefit analysis should be made before treatment with etanercept is instituted (44).

In summary, the incidence of AEs, serious AEs, infections, and serious infections with etanercept were all comparable to placebo and historical controls, with the exception of injection-site reactions (ISRs), which were more common with etanercept. However patients with chronic infections or those more prone to infections (such as patients with diabetes) are more likely to have significant difficulty with infections if etanercept is continued. Twenty cases of tuberculosis have been reported in patients treated with etanercept, some of which were miliary. A few opportunistic infections have also been reported.

Infliximab

In the controlled clinical trials of infliximab in rheumatoid arthritis (45), adverse reactions occurred in an incidence similar to its comparator, methotrexate monotherapy, other than infusion reactions (rather than injection site reactions) which occurred in 5% of patients. In clinical trials of infliximab in patients with congestive heart failure, however, patients treated with infliximab had a higher mortality rate. There was also no pre-approval, prospective, large safety trial of infliximab which evaluated the use of this agent in patients with a wide-spectrum of co-morbid diseases or in combination with DMARDs other than methotrexate. Since approval, it has become clear that reactivation of latent tuberculosis, histoplasmosis, Pneumocystis carinii, candidiasis, listeriosis, coccidiomycosis and herpes virus infections are problems with infliximab (46, 47).

In summary, the clinical trial of infliximab compared to MTX showed that there were no differences in the rate of AEs, serious AEs, infections, or serious infections other than an increase in infusion reactions with infliximab and a slight increase in cases of pneumonia in the higher dose infliximab groups. Post-marketing experience has shown that in some patients with latent tuberculosis, the infection was reactivated when they were treated with infliximab. Fungal infections, such as histoplasmosis, coccidiomycosis, listeriosis, and *Pneumocystis carinii* were also reported.

Conclusion

Serious infection, requiring hospitalization or treatment with parenteral antibiotics, has a higher incidence in patients with rheumatoid arthritis (RA) compared with the general population, even prior to the use of corticosteroids and anti-cytokine therapy. Co-morbidities, disability, and concomitant medications are some of the factors associated with this increased rate of infection. When assessing the safety profile of a therapeutic agent, it should be understood that reports from different sources will show varying rates of adverse events. Trials designed with criteria that exclude patients with co-morbid conditions or restrict the use of concomitant medications will not accurately reflect the true incidence of significant adverse events seen in the actual target population. RA patients usually have a wide range of co-morbidities and are exposed to a number of concomitant medications. Studies designed to reflect the true target population, and post-marketing pharmacovigiliance studies, are more likely to reveal the true adverse events associated with a therapy.

Traditional DMARDs, including parenteral gold, sulfasalazine, methotrexate and leflunomide have a number of toxicities which can limit their clinical usefulness. These toxicities include bone marrow suppression, hepatic inflammation, renal damage, teratotoxicity, pulmonary inflammation, apthous stomatitis and increased incidence of serious infection.

Approved biologics for the treatment of RA appear to have a relatively benign safety profile other than ISRs or infusion reactions. Patients with – or susceptible to – chronic infections may be at a higher risk of developing significant infections. When treating patients with these agents caution should be used in those who may have latent or active tuberculosis (or other fungal infections), especially with the use of monoclonal antibodies against TNF- .

Anakinra is a novel molecule with a unique mechanism of action. Its short half-life provides for flexible control of therapy. It is possible this short half-life may provide significant benefit with respect to prevention and treatment of serious adverse events. Discontinuation of anakinra when an adverse event appears may allow for a more rapid response to appropriate therapy, as opposed to other BRMs with a much longer half-life.

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