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Rheumatoid Arthritis is a disease which affects people in their prime of life, predominantly between the ages of 20-50 years of age, with a clear preference for women. The disease is quite heterogeneous with an unpredictable course; however, in general, it leads unchecked to destruction of the tissues within joints and consequent physical disability in the great majority. Therapy has been targeted to treat signs and symptoms of the disease as well as to change its natural history. Without disease modifying therapy patients with this disease do not enjoy a normal life span. Unfortunately, although there are drugs that have been shown to improve signs and symptoms, alter the natural history of the disease, and improve quality of life there is still no cure. Additionally, these available therapies are associated with risks including the potential risk of death or irreversible organ damage. The challenge for society is to balance these known potential risks of therapy with the acknowledged benefits despite the fact that these drugs do not lead to cure.

Prior to 1998 there was a limited repertoire of therapies available that fulfilled the characteristics of a disease-modifying drug (DMARD). Those therapies included cyclophosphamide, intramuscular gold, antimalarial therapy, sulfasalazine, azathioprine, 6-mercaptopurine, and methotrexate. Although available as a chemotherapeutic agent for many years, it was not until 1988 that methotrexate was popularized at relatively low dose as a chronic treatment for RA. Approval of methotrexate for improving the signs and symptoms of RA soon followed, but it was within the development program for leflunomide that both sulfasalzine and methotrexate have been most rigorously studied.

All of the available therapies to treat RA possess potential inherent risks. The non-selective nonsteroidal anti-inflammatory drugs, which are not presently thought to have important effects on the natural history of the disease, are known to induce significant damage to the upper and lower gastrointestinal track related to the primary effects of the drugs. DMARDs similarly possess risks. These risks are mostly related to the inherent

mode of action of the drug such as bone marrow suppression with cytotoxic therapies, although idiosyncratic events or direct effects of a specific drug on an organ such as heavy metal damage to the kidneys associated with gold therapy might be observed. Data accumulated during this period before 1998 demonstrated that few patients were tolerant and therapeutically responded for long periods of time. Thus, it was common for patients to require various agents during the "life" of their active disease. With the advent of methotrexate patients began to stay on therapy for longer periods. However, even the relatively low dose of methotrexate used to treat RA was associated with significant risks including infection, infiltrative pulmonary disease particularly in those patients who suffered obesity or diabetes mellitus, and chronic progressive cirrhosis with or without antecedent drug induced hepatitis. Other risks associated with other specific therapies included (1) cyclophosphamide-induced leukemia, urinary tract cancers, or bone marrow suppression leading to infection; (2) IM gold-induced heavy metal kidney damage, skin reactions, bowel disease, vasculitis; or (3) sulfasaslazine induced skin reactions and/or hepatitis.

Thus, the use of disease modifying therapy was important, the available therapies required chronic use and were not without potential toxic effects. With the advent of leflunomide there was yet another therapeutic alternative that was shown to improve signs and symptoms and in robust studies investigators demonstrated that there was also inhibition of x-ray progression. The effects of leflunomide were similar to those observed with several active comparators used in the same trials such as methotrexate and sulfasalazine.

Table 1 shows the results of several studies comparing the effects of monotherapy with leflunomide, sulfasalazine or methotrexate using the primary outcome measure for regulatory approval, the American College of Rheumatology (ACR)/ World Health Organization (WHO) responder index (ACR 20). This standard is a 20% improvement in multiple measures expressed as a composite score. In addition, the ACR 50 and 70 are also shown. These data are all extracted from the official FDA approved product description termed the "label".

Table 1. Summary of ACR Response Rates* for Leflunomide, sulfasalzine, methotrexate

Study and Treatment Group	ACR 20%	ACR 50%	ACR 70%
Placebo-Controlled Studies			
US301 (12 months)			
Leflunomide (n=178)†	52.2‡	34.3‡	20.2‡
Placebo (n=118) †	26.3	7.6	4.2
Methotrexate (n=180)†	45.6	22.8	9.4
MN301(6 months)			
Leflunomide (n=130)†	54.6‡	33.1‡	10.0§
Placebo (n=91)†	28.6	14.3	2.2
Sulfasalazine (n=132)†	56.8	30.3	7.6
Non-Placebo Active-Controlled Studies			
MN302 (12 months)			
Leflunomide (n=495)†	51.1	31.1	9.9
Methotrexate (n=489)†	65.2	43.8	16.4

* Intent to treat (ITT) analysis using last observation carried forward (LOCF) technique for patients who discontinued early.
† N is the number of ITT patients for whom adequate data were available to calculate the indicated rates.
‡ p<0.001 leflunomide vs placebo
§ p<0.02 leflunomide vs placebo

Since the approval of leflunomide, the Tumor Necrosis Alpha (TNF alpha) inhibitors have also been approved with similar benefits. As discussed in Dr. Goldkind's Medical Officer's review there are also risks of potential toxicity for methotrexate, leflunomide and sulfasalazine. The potential toxic effects of these TNF alpha biologic disease-modifying therapies include death from opportunistic infections such as tuberculosis and systemic fungal diseases. Additionally, demyelinating syndromes, autoimmune disease such as systemic lupus erythematosus, and non-Hodgkins lymphoma have been reported associated with the use of TNF alpha inhibitors.

Although not a primary issue for regulatory approval or use, it would be inappropriate in this review not to mention the wide variation in costs associated with these disease-modifying drugs and biologic therapies. Methotrexate is certainly the least expensive, with the TNF alpha inhibitors tipping the scale at over $10,000 per year per patient. Given that none of these therapies provide cure thus necessitating chronic use and no one therapy is universally well tolerated, there is a need for a multiplicity of therapeutic options to be available.

With the approval of leflunomide and the TNF alpha inhibitors either as monotherapy or in association with other disease modifying therapies, the health care community has been provided many more options than previously. However, when analyzing the benefits of each of these therapies there are remarkable similarities. Although it is inappropriate to compare directly across studies that recruit patients with differing stages of this heterogeneous disease process, it is useful to note that all of these therapies have similar effects as measured by the ACR20. (Tables 2,3,4,5 all extracted from the product label). Admittedly, there are many patients who rapidly respond to the inhibitors of TNF alpha, and fatigue in particular is readily improved and appreciated by patients although not measured within the ACR 20 directly. It is interesting to note for example that the ACR 20 responses with infliximab, a chimeric monoclonal antibody to TNF alpha, shown in table 2, are 48% but only when methotrexate is given in combination to decrease the incidence of developing neutralizing antibodies in the treated patients. Athough not as well studied with infliximab, the effects of monotherapy with etancercept (Table 3) or adalimumab (Table 4) are improved when methotrexate is given concomitantly. In the following tables 3 and 4 are shown the ACR 20 results of etanercept and adalimumab. The final table (5) demonstrates the ACR 20 responses for the recently approved inhibitor of interleukin I receptor antagonist (IL-1ra).

As can be seen, the effect sizes of difference in the ACR 20 for these therapies except for IL-1ra are all in a similar realm, ranging from leflunomide: 26%, methotrexate: 19% (almost all patients in the US studies were concomitantly treated with folic acid), sulfasalzine: 28%, 12 month data (all table 1); infliximab with methotrexate in combination: 27%, 12 months data (table 2); etanercept with combination methotrexate:

44%, 6 month data (table 3); and adilimumab monotherapy:27% and in combination with methotrexate 35% at 12 months (table 4). The effect size of the studies regarding IL-1ra are smaller ranging about 16% (table 5). It is important to consider that all of these trials recruited different patients with differing amounts of disease. Only within the leflunomide data base can the methotrexate responses or sulfasalazine responses be appropriately compared with leflunomide.

Table 2
PERCENTAGE OF PATIENTS WHO ACHIEVED
AN ACR RESPONSE AT WEEKS 30 AND 54 with infliximab

		REMICADE + MTX			
		3 mg/kg [a]		10 mg/kg [a]	
Response	Placebo + MTX (n=88)	q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)
ACR 20					
Week 30	20%	50%	50%	52%	58%
Week 54	17%	42%	48%	59%	59%
ACR 50					
Week 30	5%	27%	29%	31%	26%
Week 54	9%	21%	34%	40%	38%
ACR 70					
Week 30	0%	8%	11%	18%	11%
Week 54	2%	11%	18%	26%	19%

[a] $p < 0.05$ for each outcome compared to placebo

Table 3. The ACR 20, 50 70 responses with etanercept

	Placebo Controlled				Active Controlled	
	Study I		Study II		Study III	
	Placebo	ENBREL[a]	MTX/Placebo	MTX/ENBREL[a]	MTX	ENBREL[a]
Response	N = 80	N = 78	N = 30	N = 59	N = 217	N = 207
ACR 20						
Month 3	23%	62%[b]	33%	66%[b]	56%	62%
Month 6	11%	59%[b]	27%	71%[b]	58%	65%
Month 12	NA	NA	NA	NA	65%	72%
ACR 50						
Month 3	8%	41%[b]	0%	42%[b]	24%	29%
Month 6	5%	40%[b]	3%	39%[b]	32%	40%
Month 12	NA	NA	NA	NA	43%	49%
ACR 70						
Month 3	4%	15%[b]	0%	15%[b]	7%	13%[c]
Month 6	1%	15%[b]	0%	15%[b]	14%	21%[c]
Month 12	NA	NA	NA	NA	22%	25%

a. 25 mg ENBREL SC twice weekly.
b. $p < 0.01$, ENBREL vs. placebo.
c. $p < 0.05$, ENBREL vs. MTX.

Table 4 : ACR Responses in Placebo-Controlled Trials of Humira (Percent of Patients)

	Study II Monotherapy (26 weeks)			Study III Methotrexate Combination (24 and 52 weeks)	
Response	Placebo N=110	HUMIRA 40 mg every other week N=113	HUMIRA 40 mg weekly N=103	Placebo/MTX N=200	HUMIRA/MTX 40 mg every other week N=207
ACR20					
Month 6	19%	46%*	53%*	30%	63%*
Month 12	NA	NA	NA	24%	59%*
ACR50					
Month 6	8%	22%*	35%*	10%	39%*
Month 12	NA	NA	NA	10%	42%*
ACR70					
Month 6	2%	12%*	18%*	3%	21%*
Month 12	NA	NA	NA	5%	23%*

*$p<0.01$, HUMIRA vs. placebo

Table 5. Percent of Patients with ACR Responses in Studies 1 and 3

	Study 1 (Patients on MTX)		Study 3 (No DMARDs)		
Response	Placebo (n=251)	Kineret™ 100 mg/day (n=250)	Placebo (n=119)	Kineret™ 75 mg/day (n=115)	Kineret™ 150mg/day (n=115)
ACR 20					
Month 3	24%	34% [a]	23%	33%	33%
Month 6	22%	38% [c]	27%	34%	43%[a]
ACR 50					
Month 3	6%	13% [b]	5%	10%	8%
Month 6	8%	17% [b]	8%	11%	19%[a]
ACR 70					
Month 3	0%	3% [a]	0%	0%	0%
Month 6	2%	6% [a]	1%	1%	1%

[a] $p<0.05$, Kineret™ versus placebo
[b] $p<0.01$, Kineret™ versus placebo [c] $p<0.001$, Kineret™ versus placebo

In addition to the improvement in the signs and symptoms of RA, leflunomide, methotrexate, sulfasalzine, and the TNF alpha inhibitors all reduce the progression of x-ray damage to a similar degree in those patients who respond. Thus these drugs have proven that they modify the natural history of the process. Whether or not these therapies will continue to have such sustained effects over the entire life of a patient's disease perhaps lasting as long as 30 years is unknown. There are now longer term open label data that has been accumulated with several of these therapies which suggests that the improvement in signs and symptoms may be preserved in those patients who respond consistently for at least 5 years. However, loss of therapeutic benefit over time with all of these therapies continues to plague these patients.

In summary, each of the available disease modifying therapies, which have been shown to improve signs and symptoms while retarding x-ray progression and improving physical function have also been shown to have risks associated with their use. Although the effective size varies between therapies, and each study has included patients which are difficult to compare across studies, in general these beneficial effects are all similar. In assessing the benefit to risk ratios of these therapies, it is clear that all of these treatments are beneficial, and it is important clinically to have multiple different types of therapy available for maximal benefit to the individual patient. Dr. Goldkind's review adds the broad risk assessment discussion to provide context for the overall demonstrated benefits. It is important to consider that any one patient may benefit significantly better

than the benefit expressed within patient populations studied within a clinical trial even with a therapeutic with a relatively small effect size in a trial.

Thus, the below quote from the March 28, 2002 Citizen's petition asking for the removal of leflunomide from the market is predicated on inaccurate evidence.

"Leflunomide offers no advantages to patients with rheumatoid arthritis since it lacks any increased efficacy and appears to pose an increased likelihood of serious adverse events such as liver toxicity when compared to methotrexate, the current gold standard. …..With a variety of better drug treatments available, there is no reason to subject patients to an accumulating list of added risks; leflunomide should be promptly removed from the market."

Specifically, leflunomide offers similar advantages as the other therapies, and there is no evidence of increased overall risk associated with leflunomide as compared to the other DMARDs. Each available therapy has unique problems. Although methotrexate has been used for a longer period of time, its effects do not define it as the "gold standard" except in marketing terms. Instead its benefit to risk ratio in association with its costs and long experience are typically cited as the rationale for it to be chosen first as clinicians determine which drug to begin in any given patient requiring disease modifying therapy.

Division Assessment of NDA 20-905 supplement 6

In considering the data submitted by the sponsor to gain approval for the indication of improvement in physical function, a supplemental NDA (006) has been submitted which presents several longitudinal studies to support this claim. These studies were adequate and well controlled. The studies have been reviewed and are described below:

I. DESCRIPTION OF THE TRIALS

Trial # 1: US 301. This was a 24 month study comparing leflunomide (100mg/d x 3d, then 20mg.d) with methotrexate (7.5-15mg/wk with supplemental folate) and placebo (using a 3:3:2 ratio) by clinical (ACR20), radiographic (Sharp score) and by disability and health-related quality-of-life measures. The trial data was used for the NDA and was powered to show a one year difference of leflunomide compared with placebo. Disability was assessed using the Health Assessment Questionnaire, consisting of a self-administered list of 20 items, and also by shortened form (the modified HAQ, the mHAQ) consisting of 8 items, the results for which were entirely duplicative of the HAQ. Health-related quality-of-life (HR-QoL) was assessed using the standard SF-36, divided into the so-called physical component (SF36-PC) and mental component (SF36-MC). For ethical reasons, the design of US301 provided for mandatory, blinded reassignment of patients insufficiently responsive (protocol defined) at four months, leflunomide to methotrexate, methotrexate to leflunomide, and placebo to leflunomide.

Trial #2: MN301/303/305. MN301 was a 6 month study comparing leflunomide with sulfasalazine (2gm/d) and placebo (3:3:2) by the same three parameters as in US301. The 6 month, placebo arm was to demonstrate assay sensitivity, which it succeeded in doing for the clinical and radiographic endpoints (see NDA Medical Review, 9/1998), but not continued after. Patients in the two active arms were then asked, while continuing the blind, to enroll in a 6 month extension

study, MN303, then asked again to enroll in a 12 month extension, MN305. There was attrition at each timepoint, and these patients were considered dropouts and analyzed with LOCF.

Trial #3: MN302/304: MN302 was a 1 year study of leflunomide with methotrexate (7.5-15mg/wk without supplemental folate) by the same three parameters. Patients were then asked, while continuing the blind, to enter a one year extension, MN304. Those declining were handled as noted above in MN301/3/5.

Comparison of trials

	US301	**MN301/3/5**	**MN302/4**
Size	508	358*	999
Location	US/Can	Europe	Europe
Controls	mtx & plc	ssz & plc(6mo)	mtx
Patients			
Age (mean, yrs.)	54	59	58
Disease duration (mean)	6.8	7.0	3.7
No prior DMARDS (mean)	0.9	1.1	1.1
Percent steroid use	54%	45%	68%

- *92 assigned to placebo

II. PATIENT ACCOUNTABILITY

	US301			**MN301/3/5**		**MN302/4**	
	Lef	mtx	plc	lef	ssz	lef	mtx
Randomized	190	190	128	133	133	501	498
Completed 6 months				96	83		
Re-consenting at 6 mo							
declined				16	7		
agreed				80	76		
Completed one year	98	101	36	71	68	349	387
Re-consenting at 1 yr	(not required)						
declined				11	8	57	67
agreed				60	60	292	320
Completed two years	83	80	27	49	46	233	264
Failed to complete two years on randomized therapy	107	110	101	84	87	268	234
Total	190	190	128	133	133	501	498

III. SAFETY

The safety profile that emerged from the second year of exposure did not reveal any major departures from what was already known from the NDA and addressed in the label. Dr. Goldkind has provided a full safety review of leflunomide in his MO review.

IV. Results

The data from the first year had been evaluated in the review of the NDA 20-905. In these data the number of patients on placebo at 4 months (16 weeks) was 80% which provides an acceptable anchor for determining superiority to placebo of leflunomide for the HAQ measure. This anchor then allows the data to allow the rest of the year to be considered in terms of this outcome.

Point estimates and confidence intervals of the mean differences of leflunomide and comparator by ITT/LOCF using log regression/ANCOVA with co-variates being region, disease duration, time since last DMARD, treatment x region, treatment x disease duration, and treatment x time since last DMARD for US301, and investigator pool, disease duration and treatment for MN301/3/5 and MN302/4. Negative values for the HAQ and xray, and positive values for the SF36 and ACR20 are improvements in the point estimates for leflunomide over control.

Comparison	**HAQ**	**SF36-PC**	**SF36-MC**	**ACR20**	**XRAY**
US301-Lef vs Plc One year	-0.460 (-0.622,-0.298) p<0.001	7.844 (4.164, 10.523) p<0.001	2.032 (-1.173, 5.237) NS	26.0% (15,2, 36.8) P<0.001	-2.536 (-3.981,-1.090) p=0.001
Two year	-0.397 (-0.539,-0.255) p<0.001	6.581 (3.725,9.437) P<0.001	0.554 (-2.28, 3.435) NS	31.8% (21.7, 41.9) p<0.001	-2.711 (-4.148,-1.274) p<0.001
US301-Lef vs Mtx One year	-0.231 (-0.411,-0.050) p=0.0121	2.408 (-1.092,6.908) NS	2.415 (-0.877, 5.706) NS	6.7% (-3.6, 17.0) NS	-1.153 (-2.302,-0.003) p=0.049
Two year	-0.236 (-0.381,-0.091) p=0.002	3.955 (0.963,6.946) P=0.010	0.427 (-2.196, 3.050) NS	5.2% (-5.0, 15.3) NS	-1.186 (-2.289,-0.082) p=0.035
US301-Mtx vs Plc One year	-0.230 (-0.412,-0.048) p=0.014	5.049 (1.649, 8.449) 0.009	-0.273 (-3.460, 2.914) NS	19.3% (8.5, 30.1) p<0.001	-1.399 (-2.263,-0.236) p=0.019
Two year	-0.164 (-0.305,-0.022) P=0.023	2.729 (-0.122,6.580) NS	0.161 (-2.429, 2.751) NS	26.7% (16.7, 36.7) p=0.001	-1.592 (-0.435,-2.749) 0.007

MN301-Lef vs Ssz One year	-0.162 (-0.314,-0.010) p=0.037	XXXXXX	XXXXXX	0.1% (-12.0, 12.1) NS	-0.375 (-3.29, 2.54) NS
Two year	-0.175 (-0.330,-0.019) p=0.028	XXXXXX	XXXXXX	8.4% (-3.7, 20.4) NS	-2.916 (-7.075, 1.242) NS
MN302-Lef vs Mtx One year	0.087 (0.014, 0.160) p=0.019	XXXXXX	XXXXXX	-14.1% (-20.2, -8.02) p<0.001	2.64 (-2.68, 7.96) NS
Two year	0.106 (0.028, 0.183) p=0.008	XXXXXX	XXXXXX	-11.3% (-17.5, -5.2) p<0.001	1.312 (-0.421, 3.045) NS

Clearly, there is adequate evidence as demonstrated by changes in the HAQ (and further supported by changes in the SF-36), to suggest that in 1 year there was benefit in terms of improvement in physical function with evidence of a durable response in year two. This fact concerning the year 1 data was confirmed by the Arthritis Advisory Committee, August 2001 when it convened to review the pivotal data for approval for leflunomide. They determined that this data was compelling; however, it was recognized that the RA guidance document required a 2 year data set for the awarding of an indication for "improving disability". With the accumulation of more experience and data, it has become evident that the requirement for a 2-year double blind randomized controlled trial to achieve the indication for improvement in disability is not realistic. This is due to the inherent problem of maintaining the integrity of longer term controlled trials including patient drop out for reasons beyond toxic effects or lack of efficacy such as withdrawal of continuation in the trial for secular reasons such as moving away. The data in this table further highlights important evidence for the efficacy of leflunomide compared to the other agents studied. For example, in each study changes in the ACR 20 favored leflunomide over the comparator and in most instances these changes were statistically significant. Furthermore, in each study, x-ray changes also favored leflunomide, and again in most instances these changes were statistically significant.

Furthermore, there have been accumulated medical and legal concerns that "disability" may imply more than just alterations in "physical function". CBER has applied this same approach in the approval of infliximab and adalimumab for improvement in physical function utilizing the HAQ Disability Index as a measure for improvement in physical function based on those changes observed within a one year controlled and blinded data set.

Conclusion

In conclusion, in that there is no cure for RA, it is important to continue to provide as many therapies as possible for physicians and patients to choose among. The presently available therapies each have similar measured benefits along with identified unique risks. These risk-to-benefit ratios need to be understood by those who make therapeutic choices. This division sees utility in risk assessment and management programs, which will help educate both the clinicians prescribing these therapies as well as the patients who use them about the risks and benefits of embarking on such a treatment map. We need to continue to use the appropriate tools to be vigilant in ascertaining the benefit to risk ratio of these therapies in the future. Thus, the evidence supporting the observation that leflunomide improves physical function is shown by the following clinical trials submitted to NDA 20-905 Supplement 006:

> Trial # 1: US 301. This was a 24 month study comparing leflunomide (100mg/d x 3d, then 20mg.d) with methotrexate (7.5-15mg/wk with supplemental folate) and placebo (using a 3:3:2 ratio) by clinical (ACR20), radiographic (Sharp score) and by disability and health-related quality-of-life measures. Disability was assessed using the Health Assessment Questionnaire, consisting of a self-administered list of 20 items, and also by shortened form (the modified HAQ, the mHAQ) consisting of 8 items, the results for which were entirely duplicative of the HAQ. Health-related quality-of-life (HR-QoL) was assessed using the standard SF-36, divided into the so-called physical component (SF36-PC) and mental component (SF36-MC). For ethical reasons, the design of US301 provided for mandatory, blinded reassignment of patients insufficiently responsive (protocol defined) at four months, leflunomide to methotrexate, methotrexate to leflunomide, and placebo to leflunomide.
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> Trial #2: MN301/303/305. MN301 was a 6 month study comparing leflunomide with sulfasalazine (2gm/d) and placebo (3:3:2) by the same three parameters as in US301. The 6 month, placebo arm was to demonstrate assay sensitivity, which it succeeded in doing for the clinical and radiographic endpoints (see NDA Medical Review, 9/1998), but not continued after. Patients in the two active arms were then asked, while continuing the blind, to enroll in a 6 month extension study, MN303, then asked again to enroll in a 12 month extension, MN305. There was attrition at each timepoint, and these patients were considered dropouts and analyzed with LOCF.
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> Trial #3: MN302/304: MN302 was a 1 year study of leflunomide with methotrexate (7.5-15mg/wk without supplemental folate) by the same three parameters. Patients were then asked, while continuing the blind, to enter a one year extension, MN304. Those declining were handled as noted above in MN301/3/5.

In addition, the evidence supporting the safety of leflunomide is presented in Dr. Goldkind's Medical Officer review.