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About the REFLEX study

- REFLEX (Randomised Evaluation of Long-term Efficacy of Rituximab in RA) is a pivotal Phase III study evaluating the efficacy and safety of rituximab in combination with methotrexate (MTX) in patients with the most difficult-to-treat RA.
- Patients in the study had long-standing and severe disease and were refractory or unresponsive to one or more disease-modifying anti-rheumatic drugs (DMARDs), including anti-TNF therapies.
- Patients in the study received either a single treatment course of just two infusions of rituximab two weeks apart (1000 mg i.v. on days 1 and 15), or placebo infusions, in combination with continuing MTX and a two-week course of glucocorticoids.
- The trial was conducted across 114 centres in 11 countries worldwide (including 7 in Canada and 33 centres in Europe) between May 2003 and January 2005 and included 517 adult patients.

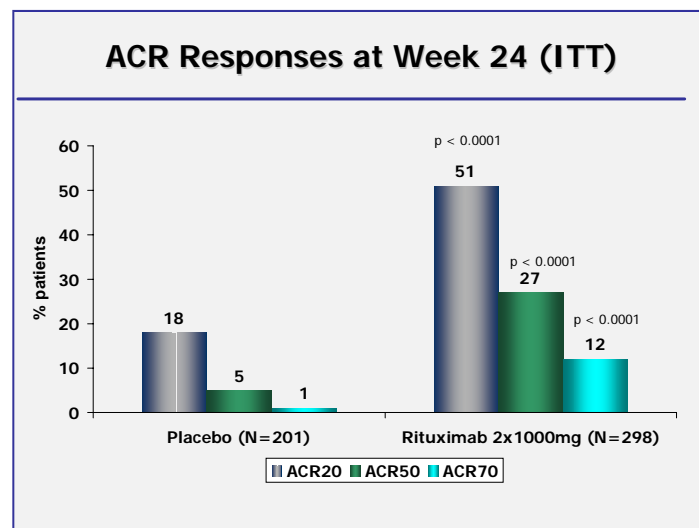
The results

- The results of the 24-week analysis show that rituximab in combination with MTX was highly effective, producing statistically significantly higher response rates compared to placebo plus MTX, with 51% of patients achieving the primary endpoint of ACR20¹ (compared to 18% with placebo plus MTX).

¹ The ACR response is a standard assessment used to measure patients' responses to anti-rheumatic therapies, devised by the American College of Rheumatology (ACR). It requires a patient to have a defined percentage reduction in a number of symptoms and measures of their disease. For example, a 20 or 50% level of reduction (the percentage of reduction of RA symptoms) is represented as ACR20, ACR50 or ACR70. An ACR70 response is exceptional for existing treatments and represents a significant improvement in a patient's condition.

- In *all* of the ACR core parameters measured to achieve the overall ACR20 response (including swollen and tender joint counts, as well as a number of different patient and physician assessments), the responses were consistently and significantly greater for patients receiving rituximab.
- Significantly more patients in the rituximab group reached the hard-to-achieve goals of ACR50 and ACR70 compared to placebo. Over five times as many patients in the rituximab group achieved ACR50 (27% compared to 5%), and twelve times more rituximab plus MTX patients achieved ACR70 at 24 weeks (12% compared to 1%).

Figure 1: REFLEX ACR Response at Six Months



- Fifteen percent of the rituximab-treated patients were considered to have low disease activity at week 24, and 9% were in clinical remission, compared to none in the placebo-treated group.
- Judged by the secondary endpoint of EULAR Response², almost three times as many rituximab-treated patients showed a good or moderate response compared to placebo (65% compared to 22%), a significant difference which was apparent at week 8, and which continued to increase through to week 24.

² The EULAR Response Score is defined as a decrease in the Disease Activity Score (DAS) of > 1.2 and a current DAS level of ≤ 2.4.

Quality of Life

- Treatment with rituximab plus MTX led to statistically significant changes on different measures of perceived improvements in all patient-reported outcomes (PROs) versus MTX alone. PROs are the improvements perceived by patients in their disease following treatment with rituximab, and include assessment of a number of areas including physical function and mental health (see Fig 2). The results support previous efficacy results from other analyses (ACR and EULAR responses and DAS28) and show that symptomatic improvements with rituximab are mirrored by improved patient outcomes.

Figure 2: Examples of Patient-Reported Outcomes

Examples of Patient-Reported Outcomes		
Summary Measures	Scales	Examples
Physical Health	Physical function	Climb flights of stairs Lift, carry groceries Bath, dress
	Role – physical	Accomplished less Had difficulty
	Bodily pain	Pain – magnitude Pain – interference
	General health	Health to get worse Health excellent
Mental Health	Vitality	Pep / life Energy Worn out
	Social functioning	Social – extent Social – time
	Role – emotional	Cut down time Accomplished less
	Mental health	Nervous Down in the dumps Happy / sad

Safety

- Overall the rituximab regimens were well tolerated, with adverse events experienced being consistent with those noted in earlier studies of rituximab in RA. The most frequently reported adverse events in the study were primarily infusion-related and mild-to-moderate in intensity, demonstrating that rituximab is well tolerated. A slightly higher frequency of serious adverse events was observed in the MTX plus placebo groups (10%) than in the rituximab group (7%).

Conclusion

- The results from REFLEX demonstrate that rituximab provides a significant and clinically meaningful improvement in all objective measures of RA disease activity at 24 weeks, and

confirm the efficacy and safety profile of rituximab seen previously in patients with RA who had failed prior DMARD therapy³, and are considered difficult-to-treat.

³ Data from the DANCER study, presented at EULAR 2005. In press.