EPILOGUE

Targeted therapies: summary clinical trials working group

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During the Symposium on Advances in Targeted Therapies two groups met to discuss issues regarding clinical trials in rheumatoid arthritis. This has been a most eventful time for rheumatology. In the past decade six biological response modifiers have been approved. There has been universal acceptance of earlier intervention to treat this disease and the success of combination therapies. And we have evidence that measuring disease activity quantitatively and adjusting drug therapy based on these measurements can improve the course of the disease, resulting in a better outcome for the patients with regard to, for instance, functional capacity and quality of life.

However, despite the significant advances in the treatment of rheumatoid arthritis, remission still is generally not an achievable goal. The discussion during this meeting addressed issues regarding current trial design and issues in therapeutic trials in rheumatoid arthritis with suggestions on how to advance the field in therapeutics. Members of the research community, including bench scientists, clinical researchers, and pharmacoeconomics specialists, and specialists from industry met to discuss issues regarding clinical trial design.

Suggestions from the working groups were as follows:

- Clinical practices throughout the world should begin to objectively evaluate patients' disease activity using quantitative instruments (validated) such as patient oriented outcome measurements, which could include functional assessments, patient or physician global assessments or activity indices such as the Disease Activity Score (DAS) or other composite measures of disease activity. This would allow for more recondite identification of patients who would be eligible for clinical trials; this in turn could assist in ease of recruitment. This would also allow for a more rigorous determination of response on prior therapies including response on methotrexate.
- In phase 2 programmes the groups felt that there should be more emphasis on mechanisms of action studies which could include biomarker studies, synovial pathology, imaging as well as potentially labelled-imaging studies. Radiographs could be incorporated at 12 weeks in phase 2 programmes, which might provide information on the ability of a drug to have an impact on erosions rather than waiting for the 52 week studies.
- There was interest in examining withdrawal trials for both phase 2 and phase 3 studies based on Crohn's disease and juvenile rheumatoid arthritis models.

- Phase 3: there was a strong consensus that trials should incorporate active comparators with a non-inferiority design. This would provide information about the efficacy and safety profile of the investigational agent versus an approved drug. This design would not have a placebo group so recruitment would be easier.
- Phase 3: in studies that use a fixed chronic methotrexate dosing design there should be mandatory withdrawal of patients who remain with defined active disease at set time points. This would eliminate the concern about the ethics of maintaining patients in 52–104 week studies on chronic methotrexate plus placebo, who might then have irreversible damage of the joints.
- Elimination of pharmacoeconomics studies from phase 3 trials was recommended and that this information should be generated from registry studies.
- There was great interest in serum, DNA, and RNA banks for future studies. A programme to allow independent investigators to apply for access to these samples should be developed. This would enhance the science of therapeutics. There are obvious hurdles in obtaining genetic material, but these barriers are surmountable.
- Liberalisation of disease activity criteria for entry was strongly recommended so that the clinical trials, particularly in phase 3, more reflect the disease activity in the clinical practice population.
- There was interest in using cohorts of patients in registries and in observational studies to look at efficacy of our currently approved treatments.
- Continued dialogue with regulatory agencies are essential to create an environment in which it will be easier to test new therapies in our current therapeutic model.
- Dialogue with specialists in other disease entities such as transplants, inflammatory bowel disease, psoriasis, oncology, was also recommended as a way to design new trials based on success in these other disease areas.

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