The EULAR meeting was held between 18th and 21st June in Lisbon, Portugal, which is situated at the most western part of Europe. Lisbon has a population of 2 million and its economy is under development. The weather was terribly unfriendly at this time of the year with a daytime temperature of over 35°C. This year, the meeting had a record number of more than 9000 participants coming from various parts of Europe and the Mediterranean countries. Because of the huge number of delegates, the conference center was always overcrowded with people and in one of the plenary lecture, more than 2500 audience clustered at the same auditorium.

The focus of the meeting was still on rheumatoid arthritis (RA). Novel data regarding the clinical efficacy of various biological agents were presented by top experts in the field. There are now three (tumor necrosis factor) TNF antagonists available in the market. Adalimumab, a fully humanized monoclonal antibody against TNFα, has been tested in major randomized controlled trials to be useful in patients with RA. Combination of methotrexate (MTX) and adalimumab is synergistic and has been shown to halt the radiological progression of the disease. The advantage of this new TNF antagonist over the existing ones such as etanercept and infliximab is that it can be administered once every other week by the subcutaneous route, which is convenient to both physicians and patients.

The broad use of the TNF antagonists in the States and Europe for RA and more recently in patients with ankylosing spondylitis raises concern regarding the risk-benefit ratio of the drugs. Professor Keystone from Toronto delivered an updated lecture on the toxicities of the TNF antagonists according to post-marketing surveys. Reactivation of tuberculosis (TB) is still a concern although the incidence has been dropping since 2001. Miliary and extra-pulmonary TB may occur and infection usually happens earlier with infliximab. Thus, pre-treatment screening for TB is essential. A chest radiograph and a PPD skin test are needed. Latent TB, if present, should be treated at the time of anti-TNF initiation. Patients with active TB should be adequately treated to resolution before the institution of TNF antagonist therapy. As TB is prevalent in Asian countries, guidelines for latent TB treatment while initiating TNF antagonists should be set by local specialists of the respective regions. Apart from TB, every kind of opportunistic infection has been reported with the use of TNF antagonists, which is expected as with other immunosuppressive therapies.

Other toxicities of long-term TNF blockade include the induction of anti-dsDNA antibodies (~15%), drug-induced lupus (rare), demyelination, triggering/exacerbating congestive heart failure and malignancies. Currently, the TNF antagonists are contraindicated for patients with moderate to severe congestive heart failure. The occurrence of malignancies is a major concern with long-term use of the TNF agents. Standardized incidence ratio (SIR) of non-Hodgkin's lymphomas is increased in patients receiving anti-TNF drugs. Therefore, close monitoring is needed.

Professor Maini presented his exciting data on a phase II randomized controlled trial of MRA, a humanized monoclonal antibody against IL-6 receptor, in patients with RA (CHARISMA study). It was demonstrated that MRA was well tolerated and effective in MTX-resistant cases of RA. Combination of MTX and MRA was synergistic. Rituximab, a monoclonal antibody against CD20, has also been shown to be effective in patients with active rheumatoid disease refractory to MTX. Again, MTX in combination with rituximab is additive in terms of efficacy. This has actually revived interest and re-visiting of the role of B cells in the pathogenesis of RA. Other newer biologics that are being tested in phase I/II trials are CTLA4-Ig, monoclonal antibodies against IL-15 and the non-depleting anti-CD4 monoclonal antibodies. There are no new data regarding the IL-1 receptor antagonist (anakinra) in the EULAR meeting.

Another area that has aroused increasing interest among rheumatologists is osteoporosis. Quite a number of sessions on osteoporosis were devoted during the EULAR meeting. Apart from conventional treatment, new and more effective bone-forming agents are becoming available in the market. Recombinant human parathyroid hormone (rhPTH[1-34]), teriparatide, is the first bone-forming agent approved by the FDA. It appears to be the most powerful anti-osteoporotic agent to date, which leads to an increase in bone mineral density (BMD) of the lumbar spine by 9.7-13.7% compared with controls. Fracture data are now available, with a significant reduction of vertebral and non-vertebral fragility fractures by 65-69% and 53-54%, respectively, in women receiving the active agent. Currently, teriparatide is recommended for high-risk patients for osteoporotic fractures, such as those who lose BMD or develop new fractures despite anti-resorptive therapy, and those who are still at high risk of fractures despite response to anti-resorptive treatment. Patients on long-term glucocorticoid treatment appear to fracture at a higher BMD and are therefore
candidates for teriparatide if there are multiple factors that put them at excessive fracture risks such as a very low T score and multiple pre-existing fractures. Besides teriparatide, strontium ranelate is another bone forming agent that is being tested in large-scale trials.

Coming back to the non-steroidal anti-inflammatory agents (NSAIDs). Newer coxibs are being marketed. These include etoricoxib (MSD), valdecoxib (Pfizer) and lumiracoxib (Novartis). Even newer NSAIDs such as nitric oxide (NO)-releasing NSAIDs (CINODs) are being developed. A new NSAID, licofelone, which blocks both the COX and LOX pathways is introduced. Apart from COX-1 inhibition, the channeling of the pathway to increase production of the leukotrienes (LT) B4 is also thought to contribute to the pathogenesis of gastropathy of the NSAIDs. Thus, blocking of both the cyclo-oxygenase and 5-lipoxygenase enzymes theoretically may reduce gastrototoxicity, while keeping the efficacy of the drug (COX-2 inhibition) without causing a loss of anti-platelet effect (COX-1 inhibition). Clinical trials have shown that licofelone is at least as effective as naproxen and celecoxib in osteoarthritis patients. The incidence of gastropathy is significantly lower with licofelone compared to naproxen. The GI safety of the drug is comparable to that of celecoxib.

Finally, the EULAR is going to introduce a 7-day course on systemic lupus erythematosus in September, 2003 in S. Miniato, Italy. Interested rheumatology trainees can go to http://database.clinexprheumatol.org/course.asp for further information.

Chi-Chiu Mok
It was my great pleasure to attend the Annual European Congress of Rheumatology held in Lisbon, Portugal between 18th June and 21st June 2003. About 8,500 participants mainly from various places of Europe attended the conference in the Lisbon Congress Centre. Historically, Lisbon became the capital of Portugal after she was conquered by King Afonso Henriques in 1147.

As in previous EULAR meetings, clinical and laboratory researches on rheumatoid arthritis (RA) remained the main theme. The opening symposium was on objectives and strategies for RA therapy and the role of TNF antagonists in advancing RA control by Professors Josef Smolen (Austria), Edward Keystone (Canada) and Paul Emery (UK). Though it has been well acknowledged that early intervention of RA patients needs early referral to rheumatologists, a recent survey of rheumatologists in Europe in 2002 demonstrated that there was no shortening of referral time of patients with new RA, with 49% of patients being referred more than 3 months into their illness. Recognition of the importance of early diagnosis of RA amongst primary health care workers was therefore stressed. Early institution of DMARDs has been found to inhibit radiographic progression. High dose methotrexate (MTX) monotherapy up to 20 mg/week within 8 weeks was shown to halt disease activity but approximately 50% of patients discontinued this treatment because of inefficacy or toxicity after 5 years. Combination therapy can be instituted using step-down, continuous or step-up approaches. There still exists controversy with regard to which approach is superior to the others. Aggressive therapy should be sustained and early short-term aggressive treatment is insufficient to obtain long-term maximum benefit.

Regarding DMARD-resistant RA, TNF antagonists, namely infliximab, etanercept and adalimumab demonstrated rapid onset of therapeutic effect either as monotherapy or concomitant therapy with methotrexate. Apart from ACR responses, TNF antagonists demonstrated substantial sustained improvement in quality of life and radiological progression. Though the use of TNF antagonists was linked to various types of infection, hematological complications, drug-induced lupus, congestive heart failure, malignancy and demyelination, these could be monitored and manageable.

Advances in immunopathogenesis of RA advocated phase II trials of IL-6 receptor monoclonal antibody (MRA), rituximab (anti-CD20) and IL-15 monoclonal antibody for the treatment of RA. A large phase II controlled trial showed good efficacy of MRA both as monotherapy and in combination with MTX. MRA was well tolerated with no adverse effect reported. In another phase II controlled trial to investigate the efficacy and safety of rituximab with or without cyclophosphamide (CTX) or (MTX), it was shown that a short course of 24-week treatment with rituximab alone, or in combination with either MTX or CTX, produced substantial and sustained improvement in disease outcome measures in patients with active RA. The combination of rituximab with MTX was safe. A double-blind, placebo-controlled trial of single doses of IL-15 monoclonal antibody in treating active RA patients showed ACR 20, 50 and 70 responses were 63%, 38% and 25%, respectively.

Besides RA, concurrent sections on other rheumatic diseases like systemic lupus erythematosus, Sjogren syndrome, osteoarthritis, osteoporosis and clinical immunology were also available in the meeting. Of interest was osteoporosis. A novel anabolic agent, hPTH(1-34) (Teriparatide), was shown in controlled trials to significantly reduce both vertebral and nonvertebral fragility fractures by 65-69% and 53-54% respectively in women with one or more prevalent vertebral fractures. In glucocorticoid-induced osteoporosis, a one year randomized controlled trial demonstrated a dramatic 11% increase in lumbar spine bone mineral density (BMD) versus 1.7% increase in estrogen-only patients after a year of teriparatide therapy. Teriparatide seems to be the "strongest" amongst other anabolic and anti-resorptive agents in rising BMD. A new concept in the treatment of osteoporosis was introduced by Professor P Delmas (Lyon). Sequential therapy with teriparatide in the first 6 months followed by an anti-resorptive agent was shown to significantly reduce the risks of non-vertebral and vertebral fractures and increase in bone mineral density. Induction therapy with a combination of teriparatide and bisphosphonate appeared to blunt BMD in animal (sheep) studies. Further data on this treatment strategy is being awaited. No incidence of osteosarcoma in relation to teriparatide use has been reported so far in human studies.

Finally, it is worth mentioned that a novel LOX/COX inhibitor, licofenlone, which blocks both the syntheses leukotrienes and prostaglandins/thromboxanes, is superior to celecoxib in gastric damage in rats. A randomized, double-blind study demonstrated that licofenlone 200 mg BD was as effective as celecoxib 200 mg QD in the treatment of osteoarthritis as noted in the improvement WOMAC pain score. Though no significant difference in GI safety was shown to favor licofenlone, worsening of peripheral oedema was significantly more frequent in the celecoxib group.

Anselm Mak