active RA who were receiving rituximab monotherapy, as well as in 5 patients receiving a concomitant DMARD other than MTX (azathioprine, cyclosporine, leflunomide), and in 10 patients who received concurrent MTX therapy. All patients received 2g of rituximab (given as individual infusions) on days 1 and 15. CD19+ B-cell percentages were analyzed at baseline, on day 15, and at weeks 4, 8, 16, and 20. Absolute B-cell numbers were calculated based on WBC. Clinical response was analyzed using DAS28 and the EULAR response score.

This report presents preliminary data for 17 of the 25 patients who have completed a 4 month follow-up period after rituximab therapy.

Thirteen (13) patients achieved an effective B-cell deletion. Full depletion (<5 residual B-cell/ul) was achieved in 100% of patients in the rituximab monotherapy group; 2 of 3 patients receiving a DMARD other than MTX; and 6 of 8 patients receiving concomitant MTX therapy. The mean absolute CD19+ C-cell counts at the point of maximum deletion were similar in all groups.

When changes in the mean percentage of naïve (CD27-IgD+) and isotype-switched memory (CD27+ IgD-), double negative (CD27-IgD-), and plasma cells (CD20-$CD19^{low}$CD38+) were further analyzed, all subtypes of B-cells were depleted including cells with plasma cell precursor phenotype (mean ±SD 52.99±16.88).

Patients receiving rituximab monotherapy achieved a mean reduction in DAS28 of 1.67 (±SD 0.76) vs 1.84 (± SD 1.44) in the MTX group and 0.7 (± SD 0.29) in the alternate DMARD group. Good to moderate EULAR clinical response was achieved by 76% of patients receiving concomitant MTX vs 55% of those receiving an alternate DMARD and 60% in those receiving rituximab monotherapy.

In this study, rituximab induced a profound depletion of the peripheral B-cell pool when administered in combination with MTX or alternative DMARDs as well as in monotherapy. The degree of B-cell depletion did not vary significantly between study groups. In all subjects residual B-cells expressed predominantly an isotype-switched memory cells' phenotype.

Patients receiving rituximab monotherapy achieved similar clinical responses compared with those receiving concomitant DMARD therapy. However, long-term follow-up data on the efficacy of rituximab monotherapy is still lacking and further analysis will show whether B-cell re-population occurs earlier in this setting.

These data suggest that rituximab monotherapy can be used effectively in patients, who – for a variety of reasons – are unable to receive adjuvant DMARD therapy.

New Therapies for Gout

A key objective of long-term management of gout is "cure". This can be achieved by patient education, modification of the patient's risk factors (diet, obesity, hypertension, lipid levels), and by maintaining tissue urate levels below the saturation point for crystal formation (serum uric acid <360 μmol/l or 6 mg/dl) [Zhang W et al. *Ann Rheum Dis* 2006].

The purine xanthine oxidase inhibitor allopurinol is the most widely used urate-lowering therapy (ULT) and offers a wide-dose range for individual dose titration. Allopurinol administered 100-900 mg daily inhibits xanthine oxidase, and thus uric acid formation. Its principal drawback is allopurinol "hypersensitivity" syndrome which is more common in patients with renal impairment. Although rare, it can prove fatal.

Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia and gout. At a daily dose of 80 or 120 mg, febuxostat was more effective than a standard fixed dose of allopurinol (300 mg/day) in lowering serum urate after 1 year (Becker MA et al. *N Engl J Med* 2005). Febuxostat is awaiting regulatory clearance in Europe. Because of its efficiency at the doses that will be available (80mg and 120mg), prophylaxis of acute attacks is recommended when initiating therapy.

Uricosurics (sulphinpyrazone, probenecid, benzbromarone) have limited availability and are contraindicated, and less effective, in patients with renal impairment. Uricosurics predominantly act on urate transporter 1 (URAT-1) in the proximal renal tubule. Benzbromarone is a very efficient urate lowering agent, even in patients with mild-moderate renal impairment, but because of rare hepatotoxicity its use has been restricted. Therefore, other ULTs are being examined. Losartan and fenofibrate cause modest reductions in serum uric acid (20-40%) via a uricosuric effect and can be adjunctive agents in gout patients that require treatment for hypertension or lipid reduction [Bardin T. *Ann Rheum Dis* 2003]. Supplementation with 500mg ascorbate/day can reduce serum uric acid in hyperuricaemic patients by close to 20% [Huang H-Y et al. *Arthritis Rheum* 2005], again through a uricosuric effect.

Humans lack uricase, the urate oxidase enzyme that converts uric acid to allantoin. When given intravenously uricase can reduce serum uric acid levels to nearly zero. There are reports of dramatic reduction in tophi using Rasburicase (a pegylated form of Aspergillus-derived uricase licensed for tumour lysis syndrome), but immunogenicity limits its repeated use. Therefore, there are current efforts to develop a less immunogenic form of mammalian uricase for repeated use in gout [Ganson NJ et al. *Arthritis Res Ther* 2006].

There are recent data from the UK showing that a minority of gout patients receive education, including dietary and other lifestyle advice and that only approximately one third are given ULT [Mikuls TR et al. *Ann Rheum Dis* 2005; Roddy et al. *Ann Rheum Dis* 2007. In press]. Of these, almost all are on allopurinol at a standard dose of 300mg/day, which is an insufficient dose for many patients, meaning that the majority of gout patients do not experience "cure" [Roddy et al]. Therefore education on the principles of long-term gout management and optimization of currently available treatments alone could have a major impact on improving the outcome of this common, painful, inflammatory arthritis.

Continued from page 9

effective and safe vaccination against a human cytokine may be achievable [Le Buanex H et al. *Proc Natl Acad Sci USA* 2006].

A number of peptide, and peptidomimetic-based approaches (such as TCR-peptide vaccines and peptides derived from heat shock protein), and antisense oligonucleotide are currently being tested in animal models to treat inflammatory arthritis.

"We have learned, and will continue to learn, a great deal about cytokines, a remarkable class of potential disease altering agents that will play a major role in future therapeutics, and lead to more 'ad personam' treatment depending upon the subtypes of diseases and the gene status." Prof. Dayer concluded.

Continued from page 21

Clinical Presentation

Clinical hallmarks include Heberden's and Bouchard's nodes, and/or bony enlargement with or without deformity affecting characteristic target joints (DIPJs, PIPJs, thumb-base, and index and middle MCPJs).

Associated Risks/Subsets

Patients with polyarticular OA of the hand are at increased risk of OA of the knee, hip, and other common target sites and should be assessed and examined accordingly. Recognised subsets with different risk factors, associations and outcomes (requiring different assessment and management) include IPJ (with or without nodes), thumb-base, and erosive OA.

Diagnosis

The differential diagnosis for OA of the hand is wide. The most common conditions to consider are psoriatic arthritis; rheumatoid arthritis, gout, and hemochromatosis. Radiographs provide the gold standard for morphological assessment of OA of the hand. Blood tests are not required for diagnosis but may be required to exclude co-existent disease.

Continued from page 28

Dr. Gossec commented, "Measuring joint space width, in particular in the semi-flexed knee, has been shown to be the most reliable and responsive way to determine structural damage severity in knee OA trials, since overall, reliability and responsiveness were higher for JSW (in particular on semi-flexed view) than for the other scoring techniques."

Prof. Wim B. van den Berg, MD, University Hospital Nijmegen, The Netherlands, provided a glimpse into the future of OA treatment via animal model studies that are exploring novel therapeutic targets in OA. Among these are IL-1 and the role of activated macrophages and degradative enzymes such as ADAMS5 and stromelysin. Novel receptors currently being investigated include the toll like receptors (TLRs) and the receptors of advanced glycation end products. TLRs are expressed on chondrocytes and synoviocytes. When activated, they drive the degradative enzymes. Advanced glycation end products are the result of non-enzymatic glycation of proteins, such as collagen. They accumulate with age and result in pathologic stiffening of cartilage and extracellular matrix.

These ongoing investigative efforts hold promise for the development of novel drugs both for the management of pain as well as retarding the OA process.