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Abatacept for lupus nephritis: no improvement in one year remission rate but faster falls in proteinuria and effects on serologic markers

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Over a third of systemic lupus erythematosus (SLE) patients have kidney involvement (lupus nephritis), and are at risk of end-stage renal disease and premature death. Current therapies are toxic and not routinely effective, so novel therapy options are urgently needed. At the ERA-EDTA Congress being held this week in Copenhagen, a study [1] will be presented in which abatacept (a selective 'T-cell co-stimulation modulator') was used to treat lupus nephritis.

Prof. David Jayne, Professor of Clinical Autoimmunity, Department of Medicine, University of Cambridge, the lead investigator: ‘Saving kidney function is the utmost priority in SLE patients. Although no improvement in the headline 1-year remission rate was achieved in this study, beneficial effects on key disease markers, including proteinuria and autoantibody levels were seen.’

Systemic lupus erythematosus (SLE) is a chronic, inflammatory autoimmune disease, in which damage is caused to multiple organs and tissues by the deposition of immune complexes [2]. Prevalence in western Europe is 25 –91 per 100,000 inhabitants. The aetiology and pathogenesis of the disease are multifactoral, but many aspects are unclear. SLE frequently causes a rash, the ‘Butterfly rash’ on the face, and kidney involvement is the most frequent severe manifestation. Current therapy with immunosuppressives and high dose glucocorticoid drugs is well established, but is toxic, poorly tolerated and not routinely effective. Approaches to management have converged with the writing of International consensus statements, including the KDIGO Guidelines [3]. Abatacept is a selective ‘T-cell co-stimulation modulator’ that blocks the activation of immunocompetent T-cells, thus inhibiting the formation of antibodies, key stages in lupus pathogenesis.

Progress in lupus nephritis therapy has been slow with no lupus nephritis Phase III trials of newer therapies demonstrating a positive effect over placebo to date. In part, this reflects the need to test new agents in addition to standard of care, and in part, inherent limitations of end point design and the heterogeneity of lupus nephritis.
ALLURE is the largest trial in lupus nephritis that has been completed. An international, randomized, double-blind, placebo-controlled phase III trial it involved over 400 patients. Sponsored by Bristol-Myers Squibb ALLURE aimed to see whether abatacept could shorten the time taken to reach remission and thereby reduce steroid exposure by evaluating the proportion of patients achieving a complete remission at one year when compared to placebo. Abatacept or placebo were given on top of standard of care with mycophenolate mofetil and steroids. The double blind period continued to two years to permit more robust assessment of efficacy and safety. Data for all patients out to one year will be presented with longer follow-up where available.

No difference in the primary end point of complete remission was seen at one year with rates of 35 and 33% respectively for abatacept and placebo treatment groups. Of particular interest, patients in the abatacept group had faster falls in proteinuria, the key biomarker of response in lupus nephritis, and reached remission earlier. There was also a trend for better recovery of renal function, GFR, in the abatacept than placebo groups. Consistent with previous studies, major differences were seen in the effects of abatacept compared to placebo on immune markers, specifically, anti-double stranded DNA antibodies and complement levels, thus confirming the predicted influence of abatacept on lupus biology. There was a trend to more infections with abatacept, matching previous experience with this drug, serious adverse events were 24% with abatacept versus 19% under placebo. However, more patients stopped placebo (22%) than stopped abatacept (14%) due to adverse events over two years. There was no difference in the number of deaths (abatacept 7, placebo 7).

Prof. David Jayne: ‘Despite failing to achieve its primary end-points the ALLURE trial has set a new standard in the design of lupus nephritis trials through its size and duration and has observed differences in key disease related markers. The disparity between effects on the biology of the disease and on disease related biomarkers, while failing to show improvements on one year remission end points remains a major challenge for assessing newer therapies in lupus nephritis. Safety and tolerability of abatacept were acceptable and were better over longer term observation. We must now wait for the complete longitudinal data after two and three years to establish whether there are any long-term differences between the groups.

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About ERA-EDTA
With more than 7,500 members, the ERA-EDTA ("European Renal Association – European Dialysis and Transplant Association") is one of the biggest nephrology associations worldwide and one of the most important and prestigious European Medical Associations. It supports basic and clinical research in the fields of clinical nephrology, dialysis, renal transplantation and related subjects. It also supports a number of studies as well as research groups and has founded a special "Fellowship Programme" for young investigators as well as grant programmes. In order to involve young nephrologists in all its activities, ERA-EDTA has created the "Young Nephrologists' Platform" (YNP), a very active committee whose board includes members who are 40 years old or younger. In addition, it has established various working groups to promote the collaboration of nephrologists with other medical disciplines (e.g. cardiology, immunology). Furthermore, a "European Renal Best Practice" (ERBP) advisory board was established by the ERA-EDTA to draw up and publish guidelines and position statements. Another important goal of the ERA-EDTA is education: The series of CME courses combined with the annual congress offer an attractive scientific programme to cover the need for continuous medical education for doctors working in the fields of nephrology, dialysis and transplantation. The association's journals, NDT (Nephrology, Dialysis, Transplantation) and CKJ (Clinical Kidney Journal), are currently the leading nephrology journals in Europe; furthermore NDT-Educational is the online educational journal of the society, with free access for all users, as well as being a very important and useful feature of the NDT-Educational "Literature Review". The ERA-EDTA Registry is a large epidemiologic database comparing countries by assessing nephrology practices throughout Europe. ENP, the European Nephrology Portal, is the latest new initiative of ERA-EDTA, where all those interested in the activities of the Society can find everything that is happening, all in one place. Finally, ERA-EDTA is a member of the European Kidney Health Alliance (EKHA), a consortium of patients, nurses and foundations relating to renal issues that actively interacts with the European Parliament. For more information, please visit www.era-edta.org