Register of Epoch-Making Biologics Hits 10 Years

BY SARA FREEMAN

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE BRITISH SOCIETY FOR RHEUMATOLOGY

BRIGHTON, ENGLAND – The arrival of biologic agents for the treatment of rheumatoid disease has been hailed as a groundbreaking event, with their practical use undeniably aided by the setup and success of large-scale biologics registers in Europe.

“I think we’ve been very privileged in the past 10 years to have lived through an era where, rather similar to the introduction of steroids, a truly epoch-making set of drugs have come to the fore,” said Dr. David Isenberg. “They have really changed the way we practice in a way that was unimaginable 15 years ago.”

Dr. Isenberg, who recently stepped down as the chair of the BSRBR (British Society for Rheumatology Biologics Register) Steering Committee, added that “one very important aspect of the way in which these new drugs have been introduced is the growth of the biologics registers, which have been developed to monitor their use.”

Started in 2001, the BSRBR has now become the largest of the European biologics registers, with data still being collected on more than 20,000 participants with rheumatoid arthritis, of whom around 15,000 are receiving anti–tumor necrosis factor–alpha agents.

A year after the register started, the UK, National Institute for Health and Clinical Excellence (NICE) published guidelines on the use of biologics and recommended that all patients who start treatment with one of the older anti-TNF agents included in the register (infliximab, etanercept, adalimumab) are eligible for inclusion into the new cohort. Former patients entering the register will then be compared with the anti-TNF control cohort.

“The BSRBR is one of the few biologics registers to include a control arm of the standard therapy of the time (nonbiologic DMARDs). Because of changing baseline characteristics and anti-TNFs themselves becoming established therapy, however, recruitment into a second, anti-TNF cohort arm has just begun. Patients who start treatment with one of the older anti-TNF agents included in the register (infliximab, etanercept, or adalimumab) are eligible for inclusion into the new cohort. Former patients entering the register will then be compared with the anti-TNF control cohort.”

“Registers are epidemiologic cohort studies dedicated to pharmacovigilance and real-life effectiveness,” commented Dr. Angela Zink, one of the key people involved with the running of the BSRBR. “At the end of the day it works because everyone benefits,” he said. The companies essentially get 5 years of follow-up data on their products while the researchers are able to publish their findings in the top rheumatology journals. In addition, “the BSR gets the kudos of running the world’s largest biologics register.”

The BSRBR is funded by a grant from the BSR. The BSR receives funding from Abbott Laboratories, Boivitrum/SOBI, Merck Sharp & Dohme, Pfizer, Roche, and UCB. This income finances a separate contract between the BSR and the University of Manchester that runs the BSRBR. All decisions concerning data analysis, interpretation, and publications are made autonomously of any industrial influence. Dr. Isenberg and Dr. Symmons declared that they had no personal conflicts of interest. Dr. Zink has received research grants from Abbott, Amgen, Bristol-Myers Squibb, Essex Pharma, Pfizer, Roche, and UCB.

Family Study Identifies Possible Factors Involved in RA

BY SHARON WORCESTER

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

Unaffected first-degree relatives of patients with rheumatoid arthritis have an increased number of known risk factors for RA, compared with unaffected controls. However, the prevalence of risk factors in relatives does not equal that seen in patients, according to Dr. Lotta Ljung, senior consultant rheumatologist at Umeå (Sweden) University Hospital.

For example, the unaffected relatives had a significantly greater prevalence of anti-CCP (cyclic citrullinated peptide) protein IgG, IgA, and IgM antibody isotypes and rheumatoid factors of IgM and IgA isotypes than did the controls, Dr. Ljung said at the meeting, noting that she was not involved in the research. She gave the presentation for researcher Lisbeth Arlestig, Ph.D., a student at Umeå University, the scheduled presenter who was unable to attend.

The findings could lead to better understanding of the factors that affect rheumatoid arthritis (RA) development. Because the etiology of RA is still unknown and autoantibodies are common in patients affected with RA (and the anti-CCP antibodies discussed appear to be involved in the pathogenesis of the disease), it is of interest to analyze the prevalence, concentrations, and pattern of antibodies in first-degree relatives in multicase families, according to Dr. Ljung. The lead author was Dr. Solbritt Rantapää Dahlqvist, also of Umeå University.

The investigators set out to evaluate serologic risk markers for the development of RA in relation to genetic and environmental risk factors. They compared serologic findings of RA patients, unaffected relatives, and healthy controls. The researchers found that in 196 individuals with RA and 156 first-degree relatives from 61 multicase families compared with healthy controls, respectively, the median concentrations of the anti-CCP isoforms were 237.0 AU/mL and 2.1 AU/mL vs. 1.5 AU/mL for IgG anti-CCP; 3.4 AU/mL and 1.0 AU/mL vs. 0.6 AU/mL for IgA anti-CCP; and 53 AU/mL and 28.5 AU/mL vs. 18.5 AU/mL for IgM anti-CCP. The median concentrations of rheumatoid factors were 134.5 mcg/mL and 5.2 mcg/mL vs. 4.3 mcg/mL for IgM RA and 237 mcg/mL and 1.4 mcg/mL vs. 1.0 mcg/mL for IgA RA.

The investigators also found that RA patients were significantly more often SE (shared-epitope) positive than were unaffected relatives (71.4% vs. 53.6%; P < .001), but had similar rates of carriage of the PTPN22 variant (47.7% vs. 45.4%). Both patients and relatives had the variant at higher rates than did controls. Thus, it appears that SE is more important for the development of RA than is the PTPN22 variant, they said.

“The environmental factor of smoking was also more common among the patients and is shown to be an important risk factor” in univariate but not multivariate analyses, they noted. Indeed, 58% of patients, compared with 46% of relatives, were smokers. Also, IgG and IgA anti-CCP were significantly associated with SE in the patients, but not in the relatives. Overall, the RA patients had more risk factors for RA than did the relatives (median, four vs. three; P < .001).

The vast majority of RA patients (93%) had at least three risk factors, whereas only about half (33%) of the relatives had at least three risk factors. Risk factors here defined as anti-CCP antibodies, RF, SE, PTPN22 variant, smoking, and age.

The investigators said they had no relevant financial disclosures.