A Fifty-Two-Week, Randomized, Placebo-Controlled Trial of Certolizumab Pegol in Nonradiographic Axial Spondyloarthritis

BACKGROUND:

- Axial spondyloarthritis (SpA) is a chronic inflammatory disease predominantly affecting the sacroiliac joints and spine.
- Conventional therapy for axial SpA comprises nonpharmacologic management (physical therapy) and NSAIDs as first-line therapy.
- For patients that have active disease or objective signs of inflammation despite treatment with NSAIDs, treatment with anti-tumor necrosis factor agents has been recommended.

OBJECTIVE:
The study was undertaken to investigate the effects of certolizumab pegol (CZP), an anti-tumor necrosis factor treatment, in patients with non-radiographic axial SpA with objective signs of inflammation.

METHODS

- **Design**: multi-center, double-blinded, randomized, parallel, placebo-controlled trial
- **Duration**: 52 weeks
- **Inclusion criteria**:
    - Age $\geq$ 18 years
    - Have a documented diagnosis of adult-onset axial SpA, meeting the ASAS classification criteria
    - Have $\geq$ 12 months of symptoms duration
    - Have active disease at screening and baseline (defined as a BASDAI score of $\geq$ 4 and spinal pain score of $\geq$ 4 on a 0-10 scale despite treatment with NBBMs including $\geq$ 2 NSAIDs
    - Objective signs of inflammation
- **Exclusion criteria**:
    - Patients with radiographic sacroiliitis meeting the modified New York classification criteria
- **# patients enrolled**: n = 317; placebo + NBBM n = 158, CZP + NBBM n = 159
- **Drug regimens/dosages used**: CZP was given at a dose of 400mg divided into 2 doses at weeks 0, 2, and 4 (loading dose) followed by 200mg every 2 weeks
- **Primary outcome measures**: a composite outcome measure was achieved if all of the following 3 criteria were fulfilled:
    1. The patient remained in the study until week 52
    2. The patient continued taking double-blind study treatment throughout
    3. The patient achieved major improvement (MI) in the Ankylosing Spondylitis Disease Activity Score (ASDAS) (23) at week 52
- **Secondary outcome measures**:
    - Achievement of 40% improvement according to the ASAS (ASAS40) at weeks 12 and 52
    - Change from the baseline BASDAI score at weeks 12 and 52
    - Change from the baseline Bath Alkylating Spondylitis Functional Index (BASFI) score (26) at weeks 12 and 52
    - The Spondyloarthritis Research Consortium of Canada (SPARCC) score for sacroiliac joints (27) at week 12
    - The Ankylosing Spondylitis Quality of Life (ASQoL) score (28) at week 52
    - Nocturnal back pain at week 52
    - The number of patients who had new or recurrent anterior uveitis flares at week 52
- **Power**: 95% - this was calculated to be possible with 150 patients per group (300 patients total)
- **Data handling method used**: intent-to-treat

RESULTS

- **Number of patients who completed study**: 179 patients completed the double-blind study total
    - 54 patients in the placebo + NBBM group
    - 125 patients in the CZP + NBBM group

- **Primary outcome measure**: The primary endpoint, ASDAS-MI at week 52, was reached by 47.2% (75/159) of CZP + NBBM patients and 7.0% (11/158) of placebo + NBBM patients.
- **Authors conclusion**: Adding CZP to background medication is superior to adding placebo in patients with active non-radiographic axial SpA. These results indicate that remission in non-radiographic axial SpA treated without biologics occurs infrequently, demonstrating the need for treatment beyond non-biologic therapy.

STRENGTHS

- Data was found to be statistically significant
- Randomized, double-blind, parallel study
- 95% CI
- Sufficient duration
- Most open-label switches were done after the 12 week mark

LIMITATIONS

- Potential bias was a concern – 3 of the investigators worked for UCB Pharma
- No data was provided to account for adherence
- Doses of NBBMs were not capped or controlled
- All NBBMs were grouped as “NBBMs” whether they were NSAIDs, analgesics, DMARDs, etc.
- Extensive exclusion criteria
- Hierarchy of study endpoints was used
- Placebo-controlled
- Potential unblinding

CONCLUSIONS

- The important weaknesses of this study include the potential conflict of interest resulting from the 3 investigators that work for UCB, which is the manufacturer of the drug of interest. Also, the extensive exclusion criteria makes it difficult to extrapolate the data to real-life situations for patients with nonradiographic axial SpA. Grouping NSAIDs, analgesics, csDMARDs, DMARDs, hyaluronic acid, and corticosteroids into one category of “NBBMs” and allowing these medications to be taken during the trial is a major weakness since these drugs do not have the same mechanism of action and therefore, potential benefit for the disease-state at hand.
- The important finding that should be taken away from the study is the ASDAS-MI score at week 52 was achieved in 47.2% of CZP + NBBM patients which was significantly greater than the 7.0% of placebo + NBBM patients.
- Certolizumab pegol is a potential treatment option for patients with nonradiographic axial spondyloarthritis. After this trial, I believe that CZP should be considered as a later treatment option rather than first- or second-line. By comparing the drug to placebo, it would be difficult for this trial to show any different outcomes than it did.
- Further research should be conducted comparing CZP to another biologic instead of placebo. The study should have a lesser exclusion criteria in order to better represent the patients that may be requiring this treatment option. Also, putting limitations on the NBBMs that are allowed as well as capping the maximum doses on these medications should be considered.

Reference: Deodhar, A., Gensler, L. S., Kay, J., Maksymowych, W. P., Haroon, N., Landewé, R., Heijde, D. V. A Fifty-Two-Week, Randomized, Placebo-Controlled Trial of Certolizumab Pegol in Nonradiographic Axial Spondyloarthritis. *Arthritis & Rheumatology*. 2019; doi:10.1002/art.40866.

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