Focus on Rheumatoid Arthritis

Rheumatoid arthritis (RA), the most common inflammatory polyarthritis, is a heterogeneous chronic inflammatory disease characterized by symmetric and peripheral polyarthritis. Bone and cartilage destruction due to uncontrolled inflammation results in joint damage and physical disability requiring a multidisciplinary team approach for patient management. Most of the joint damage occurs early in the disease process and patients have a variable presentation in terms of age of onset, degree of joint involvement, and disease severity.

With multiple approved therapies, most assets in the current RA pipeline are in mid-late phase development. There are 50 assets in the RA pipeline – 13 (Phase I), 29 (Phase II), 7 (Phase III), and 1 (Pre-registration Phase).

Late-stage Assets with Recent Efficacy Data:

Olokizumab (IL-6 antagonist, Phase III/R-Pharm):

- Demonstrated encouraging efficacy and likely to be approved for moderately to severely active RA by 2022, in the US and EU.
- In the recent Phase III CREDO 3 study, olokizumab 64 mg q4w and q2w, demonstrated significant efficacy vs. placebo on multiple endpoints including ACR20 (59.6%, p=0.004; 60.9%, p=0.0029 vs. placebo 40.6%), DAS28 CRP<3.2 (28%, p=0.0035; 39.9%, p<0.0001 vs. placebo 11.6%), and ACR50 (32.3%, p=0.0054; 33.3%, p=0.0041 vs. placebo 15.9%) at week 12, respectively. However, the efficacy of olokizumab on the above endpoints was higher in a previous Phase III study (CREDO 1).

Otilimab (GM-CSF antagonist, Phase III, GSK/MorphoSys):

- In a Phase IIb study, otilimab in combination with methotrexate, demonstrated significant change from baseline vs. placebo on multiple endpoints including DAS28 CRP (–1.87 vs. –0.6, PSD = –1.27, p<0.001), CDAI (–23.23 vs. –6.59, PSD = –16.63, p<0.001), pain (–25.01 vs. –7.07, PSD = –17.94, p<0.01), and PGA (–23.9 vs. –6.72, PSD = –17.18, p<0.001) endpoints at week 12.
- Additionally, 51% of patients achieved ACR20 response vs. 11% for placebo, PSD = 40.5, p<0.001 and good/moderate EULAR response was achieved by 76% of patients vs. 22% for placebo, PSD = 54.1, p<0.001.

BCD-089 (IL-6R antagonist, Phase III, Biocad):

- In the Phase III SOLAR study, BCD-089 + MTX vs. placebo + MTX demonstrated significant efficacy on ACR20 (71% vs. 40%, PSD = 30%, p=0.0003), and LDA (52% vs. 6%, PSD = 46%, p<0.0001) at week 12.
- In the Phase II AURORA study, BCD-089 QW + MTX and BCD-089 Q2W + MTX vs. placebo + MTX demonstrated significant efficacy on ACR20 (77.1%, 57.1% vs. 17.1% for placebo, p<0.001), ACR50 (51.4%, 31.4% vs. 5.75 placebo, p=0.001), ACR70 (28.6%. 20% vs. 2.9% for placebo, p=0.0106), and DAS28 CRP<3.2 (57.1%, 28.6% vs. 2.9 for placebo, p<0.0001), at week 12.

SM03 (CD22 antagonist mAb, Phase III, SinoMab):

- In a Phase II study, SM03 600 mg (6 infusions) + MTX demonstrated significant efficacy vs. Placebo + MTX on ACR20 (65.3% vs. 34%, p=0.002), ACR50 (44.9% vs. 17%, p=0.003), ACR70 (18.4% vs. 4.3%, p=0.03), and EULAR good/moderate response (75.5% vs. 40.4%, p<0.001) at week 24.

Of all the late-stage assets, olokizumab is the most promising based on Phase III efficacy data from the CREDO 1 study and could establish a new benchmark for ACR20, ACR50, and DAS28-hsCRP ≤ 3.2 endpoints in moderately to severely active RA inadequately controlled by methotrexate therapy.

The currently available therapies control acute inflammation and flares. However, effective control of chronic inflammation remains an unmet need, and patients may continue to have smoldering disease with adverse outcomes. Some early phase MoAs such as PD1 agonism, LY3462817 (Eli-Lilly), and HDAC inhibition CKD-506 (Chong Kun Dang Pharma) may have a role in addressing chronic inflammation.

Key questions that remain to be answered:

- How to diagnose patients in pre-RA or early phases of RA to control early inflammation that is responsible for joint damage and disability?
- Will novel biomarkers/genetic markers help in early diagnosis of RA and identification of patients at risk of poor outcomes?
- How can we reduce the burden of comorbidities such as cardiovascular disease (CVD), and venous thromboembolism (VTE), which are attributed to the underlying systemic inflammation?
- What is the best way to effectively manage patients who fail or show inadequate response to a given biologic agent, and typically show lower response rate when switched to another biologic agent?

Sources: 1. ClinicalTrials.gov; 2. Company Websites; 3. Taylor PC. Clin Med. 2020;20(6):561–564

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