SYNACT PHARMA

INFLAMMATION RESOLUTION

Dr. Alan Kivitz
A Clinical Perspective on RA

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Approach to first-line therapy

- Treatment goals have changed with advent of new classes of RA therapy
- Goals are now disease remission (lack of activity) or low-level disease activity
- With multiple treatments and classes of therapy, first-line therapy has become more aggressive – treat early to have maximum impact on the course of disease

Approach to first-line therapy with methotrexate

- **Treatment goals have changed with advent of new classes of RA therapy**
- **Goals are now disease remission (lack of activity) or low-level disease activity**
- **With multiple treatments and classes of therapy, first-line therapy has become more aggressive – treat early to have maximum impact on the course of disease**
- **Will start everyone on methotrexate (MTX) unless there are contraindications**
  - MTX is an oral or injectable anti-metabolic therapy that has been available for decades and had its first use as an anti-cancer therapy
  - It is used in lower doses in autoimmune or inflammatory diseases like RA as means to suppress immune activity
- **Will allow 12-weeks of MTX therapy to judge the patient's response to therapy**

Approach to first-line therapy in patients with poor prognostic indicators

- **Poor Prognostic indicators (PPI) are factors that when identified in a patient's presentation could indicate a more aggressive or severe disease course**

- **Presenting with highly active disease is the recognized PPI for both the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) treatment guidelines**

- **In addition to presenting with highly active disease, commonly used PPI can include:**
  - **Rheumatoid factor (RF)** and or **Anti-citrullinated protein antibodies (ACPAs)** – two types of antibodies detected in blood that can attack your body and inflame your joints
  - Evidence of **joint erosions** in inflamed joints

- **In patients with PPI, will look to treat immediately with MTX and move quickly to next line of therapy which in the US is typical a biologic therapy (anti-TNF or other anti-cytokine therapy) and in Europe a biologic therapy or a JAK kinase inhibitor**

Approach to RA therapy is a benefit Vs risk assessment

- **In establishing RA therapy, a rheumatologist conducts a benefit and risk assessment of the therapy for each patient**
- **There can be a risk to long term therapy with the RA medicines in the form of toxicity and side effect issues**
- **But there is also a risk to leaving active inflammation uncontrolled:**
  - Uncontrolled disease activity leading to joint damage and disability
  - Increased cardiovascular risks for heart attack and stroke
  - Increased risk of cancer such as lymphoma
- **Need to find the balance between side effects with the medicine used to suppress the inflammation and the risk of letting inflammation go uncontrolled**

Need for new oral therapies particularly in patients with PPI

- **Current oral therapies after MTX or other DMARDSs are currently limited to the JAK kinase inhibitor class of therapies**

- **In the US JAK inhibitors have black boxed warnings of increased:**
  - Rate of infections, some of which can be 'opportunistic' can be fatal in rare cases
  - Risk of new onset cancer, major adverse cardiac events (MACE) and thromboembolism (blood clots that can be dislodged and cause stroke or pulmonary difficulty
  - Has resulted in a US restriction to use only after a trial of an anti-TNF agent and in a European restriction to not use in elderly or high-risk patients
  - As any therapy does not work equally well in all patients – not all patients respond, and the toxicity profile of the medications we use

- **New oral therapies without these significant toxicities that would not have a line of use restriction would be a welcome addition**

Incomplete responses to DMARD therapy (DMARD-IR)

- **Every patient is unique and while initial DMARD therapy can work long-term in some patients, not all patients will respond or respond well enough**

- **Incomplete responses to DMARD therapy (DMARD-IR) can present as:**
  - Patients who never really had meaningful response
  - Patients who had an initial response but still have active disease despite DMARD therapy

- **After initial DMARD therapy of ~3 mo, patients are actively involved in next decisions:**
  - Some DMARD-IR patients will be satisfied with their level of improvement and may not accept the risk of going to more aggressive therapies
  - Some patients will accept the risk of a new therapy for the chance of a better response
- **Longer term responsiveness to DMARD therapy is also variable with some patients doing well for long periods of time and some patients losing part or all of their response as their disease progresses**

Shortcomings of current therapies for DMARD-IR

- Toxicity issues with current DMARD-IR therapies are their key limitation
- Biologic therapies and oral JAK inhibitors are associated with increased rates of infections some of which can be serious, a risk which can exclude many patients
- There is room for new medications like AP1189 that may have improved safety profiles but still retain sufficient efficacy for patients who need additional options
- The initial clinical results have been encouraging for AP1189 and warrant further development to learn the answer key clinical questions about appropriate positioning
- With any new therapy, access to the drug is key especially for first-line use
- A 3-mo treatment with DMARD therapy is required in the US by most payors before you can move to another class of therapy

Need for new therapies therapies for DMARD-IR

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Potential for AP1189 in inflammatory diseases beyond RA

- **Mechanisms of action like AP1189 can potentially have utility in other inflammatory conditions beyond RA given the underlying nature of the inflammation that is common to these diseases**

- **While there is no clinical data, theoretically AP1189 could have utility in other diseases like:**
  - Psoriatic arthritis – a form of arthritis that involves primarily the joints and skin
  - Ankylosing spondylitis – an inflammatory disease that can create fusions to vertebrae in spine
  - Systemic lupus – a disease that effects the joints and that can affect numerous other systems
  - Sjogren's syndrome and other autoimmune conditions