IL-23 Update

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Outline
Examine the role of IL-12 and IL-23 in the pathogenesis of psoriasis
Highlight differences between IL-12/23 blockade and IL-23 therapeutic antibodies
Analyze available data for IL-23 inhibitors
Consider differences between agents within and across classes

Disclosures
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Abbvie, Athenex, Boehringer Ingelheim, Bond Avillion, BMS, Celgene, Dermavant, Incyte, LEO, Lilly, Novartis, Janssen, Ortho Dermatologics, Sanofi/Genzyme, Pfizer, Regeneron, SUN, UCB, MC2, Pellepharm

Background
Our understanding of the pathogenesis of psoriasis is changing with a better understanding of its immunopathogenesis
Pathogenesis of Psoriasis

IL-12 and IL-23

Ustekinumab
- FDA approved for moderate to severe plaque psoriasis and psoriatic arthritis
- Initially approved in 2009
- Over 5-year safety data available
- Long term data shows durable effect
- Very low rate of antidrug antibody formation

How safe is Ustekinumab?
- 3117 patients through Phase 2 trials and Phase 3 trials (PHOENIX 1/2, ACCEPT) and PSOLAR Registry Data
- No cases of TB or systemic fungal infection
- Serious infections at a rate of 1.1 per 100PY
- Rate of discontinuation due to infection is less than 1%
PSOLAR Registry Data

What about IL-23 Blockade?

Is IL-12 blocking bad?
Why IL-23 Blockade?

IL-23 is the primary effector of inflammation in both colitis and skin disease

- mRNA in lesional vs non-lesional skin shows same levels of IL-12 in both and increased IL-23 in lesional psoriasis skin only

More specific targeting can provide greater efficacy with reduced side effects

IL-12 shown to be important in immunity against TB, Candida, and Salmonella

Theoretical effects on tumorigenesis

IL-12 in tumor immunity

Although there are interactions between IL-12 and IL-23, there is increasing evidence that these cytokines modulate divergent immunological activities. Other than promoting the cytokine function of NK cells, IL-12 plays a development of Th1 cells via the activation of STAT4. These cytokines also producing Th1 cells are crucial for antitumor and antitumor responses (7). The role of IL-12 and Th1 cells to modulate IFN-γ in antitumor immunity has been demonstrated (8 and 9) and extensively reviewed elsewhere (10 and 11). In addition, Th1 cells and antitumor effector T cells, IL-12 and IFN-γ also inhibit the expansion of intratumoral T regulatory cells (Treg) and increase expression of tumor microenvironment, thus enhancing tumor control (8). More recently, engineered antitumor-specific CD8+ T cells expressing IL-12 have also been shown to suppress the growth of the poorly immunogenic murine melanoma tumor by generating immune responses in melanoma-specific T cells and enhancing tumor microenvironment, as well as NkY-dependent manner. Similarly, the antitumor response induced by the IL-12-expressing CD8+ T cells also improved the presence of both T cells and NK cells (12). Another study on IL-12-producing IL-10 metastatic melanoma showed that NKG2D+ TILs cells could induce tumor suppression independently of IFN and IL-12 (13). Clearly, the mechanism of IL-12-mediated tumor suppression is context-dependent. Consistently, the role of NKG2D+ cells may play an important role in inhibition tumor. IL-12 production in colorectal cancer and anti-NKLy-cells deficient mice challenged with methylycholriderine (MCA) have also shown increased role and frequency of extracellular growth of prostate-specific antigen-positive tumors in suppressing a role of endogenous IL-12 and IFN-γ in protecting the host from the emergence of chemical carcinogens induced and possible skin tumors (14 and 15).

How does this help us?

Patients ask about risk of malignancy

The present results suggested that IL-23 may be a potential prognosis marker and target for the treatment of breast cancer patients.
IL-23 Inhibitors

- Guselkumab
- Tildrakizumab
- Risankizumab

Guselkumab

- Anti-IL23p19
- Entered Phase 3 trials in 2014
- Approved July 2017 for Psoriasis
- Approved July 2020 for Psoriatic Arthritis
- 100mg q8w dosing (after loading)
- Fully human monoclonal antibody

![Graph showing percentage of patients achieving PASI 75 response](image1.png)

Proportion of patients who achieved PASI 75 response

Week 16: P<0.001 vs. ADA
Week 24: P<0.001 vs. ADA


![Graph showing percentage of patients achieving PASI 90 response](image2.png)

Proportion of patients who achieved PASI 90 response

Week 16: P<0.001 vs. ADA
Week 24: P<0.001 vs. ADA

Switching Therapy

If I have a patient on ustekinumab who wants some further improvement, should I change to a different class?

- Is guselkumab an option in these cases?

**NAVIGATE Study Design**


**Figure 1. Proportions of Patients With IGA Score of 0 or 1 and ≥2 Grade Improvement (From Week 16) at Weeks 28 and 52; Randomized Patients**

Figure 2. Proportions of Patients With PASI 90 at Weeks 28 and 52; Randomized Patients

- **Week 28**
  - Guselkumab (n=135): 48.1%
  - Ustekinumab (n=133): 22.6%
  - *P<0.001 vs. ustekinumab

- **Week 52**
  - Guselkumab (n=135): 51.1%
  - Ustekinumab (n=133): 24.1%
  - *P<0.001 vs. ustekinumab


**Guselkumab vs. Secukinumab**

- PASI 90 at Week 12:
  - Secukinumab – 76%
  - Guselkumab – 69%
- PASI 90 at Week 48:
  - Secukinumab – 70%
  - Guselkumab – 84%

*PASI-75 superiority margin not met

**How close are these medications?**

**Guselkumab vs. Ixekizumab**
What about axial disease?

Guselkumab for Psoriatic Arthritis

Take-home Messages
- IL-17 inhibitors are, on average, a bit faster than Guselkumab
- Long-term average clearance rates for newer drugs are very similar
- Guselkumab was effective in treating psoriatic arthritis, with ACR 50 rates similar to existing TNF and IL-17 inhibitors
  - Radiographic progression?
Tildrakizumab

- Anti-IL23p19
- Entered Phase 3 trials in 2012
- 100mg q12wk dosing (after loading)
- Recombinant humanized mouse monoclonal antibody

Tildrakizumab Treatment Outcomes

Long-term data (enriched population)

Tildrakizumab Psoriatic Arthritis Phase IIb
Risankizumab
Anti-IL23p19
Entered Phase III in 2016
Approved April 2019 for Psoriasis
150mg q12wk dosing (after loading)
Fully human monoclonal antibody
What’s the catch?

Risankizumab for Psoriatic Arthritis

Phase III trials completed
Top-line results reported
Sharp/Van der Heijde scores not significantly better than placebo (p=0.496)

Risankizumab vs. Secukinumab
So what are the differences?

Safety data is very good across the board
- Cases of nasopharyngitis, URI (related to efficacy?)

Efficacy is quite strong
- Average PASI improvements of newer medications (2015-on) are usually 92%+
- Patient characteristics and individual response likely a bigger driver than drug/class differences

Dosing regimens — frequency of injections
- Insurance coverage
- What about IBD?

The IBD Story

There have been some concerns about the blockade of IL-17 with regards to IBD/Crohn’s Disease

Crohn’s Disease and Secukinumab

What about IL-23 blockade?
The IBD Story

IL-17 blockade in some cases can worsen Crohn’s Disease while IL-23 blockade is a promising treatment for Crohn’s Disease.

Across large numbers of treated patients, there does not seem to be a strong safety signal with regards to Crohn’s Disease, but prescribers have likely been avoiding IL-17 inhibitors in patients with a history or strong family history of IBD.

Summary

IL-23 is involved in the pathogenesis of psoriasis.

Therapeutic antibodies targeting IL-23 are very effective in treating psoriasis, with attractive dosing regimens, long-term sustained efficacy, safety, and time to relapse.

While they are better than placebo at treating psoriatic arthritis, given the mixed data about progression of joint disease and axial involvement, IL-23 inhibitors are not ideal first-line treatments for severe joint disease.

There are some theoretical safety/risk benefits of selecting an IL-23 inhibitor over other new classes of biologics.

Thank you!

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