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Summary

GUSELKUMAB, AN IL-23P19 SUBUNIT–SPECIFIC MONOCLONAL ANTIBODY, BINDS CD64 ON THE SURFACE OF IL-23-SECRETING MYELOID CELLS, CAPTURES LOCALLY PRODUCED IL-23, AND DELIVERS IL-23 TO INTRACELLULAR COMPARTMENTS

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Guselkumab, but not risankizumab, binds CD64 on IL-23-producing myeloid cells in addition to neutralizing IL-23, which may contribute to therapeutic differences between these anti-IL-23p19 monoclonal antibodies in inflammatory bowel disease.

KEY POINTS

- Guselkumab is a fully human IgG1 antibody with a native Fc region that binds Fcγ receptors, whereas risankizumab has a mutated Fc region designed to prevent Fcγ receptor binding.
- Both antibodies displayed comparable picomolar binding affinity for IL-23 and equivalent high potency for inhibiting IL-23-induced STAT3 phosphorylation.
- Only guselkumab showed strong binding to CD64 and was able to bind CD64-positive IL-23-producing inflammatory monocytes while simultaneously capturing endogenous IL-23 secreted from those cells.
- The guselkumab-IL-23 complex bound to CD64-positive inflammatory macrophages was internalized in a time-dependent manner, mediating delivery of IL-23 to low-pH intracellular compartments.
- The authors hypothesize that guselkumab may be locally enriched in inflamed intestinal tissue where CD64-positive IL-23-producing myeloid cells are increased, potentially enabling dual action by neutralizing IL-23 at its source and mediating its removal from tissue.

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