Long-Term Care Updates

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Mirikizumab - a new treatment option for moderate to severe ulcerative colitis

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Indications:

Mirikizumab is FDA-approved for the treatment of adults with moderately to severely active ulcerative colitis (UC).[1]

Pharmacology:

Mirikizumab is a humanized IgG4 monoclonal antibody that acts as an antagonist of interleukin-23 (IL-23). It selectively binds to the p19 subunit of human IL-23 cytokine, inhibiting the ability of IL-23 cytokine to interact with the IL-23 receptor. This receptor is involved in mucosal inflammation and affects T cell differentiation, expansion, and survival. Animal research shows that inhibition of IL-23 receptors can reduce intestinal inflammation.[1]

Pharmacokinetics:

Mirikizumab's pharmacokinetic parameters are described in Table 1. Pharmacokinetic research shows that mirikizumab exhibits linear pharmacokinetics, and exposure to mirikizumab increases in a dose proportional manner. No accumulation of mirikizumab was observed over 4 weeks of subcutaneous administration. Injection site location does not appear to alter mirikizumab's bioavailability. Additionally, age, body weight, sex, race, and mild or moderate renal impairment do not appear to alter mirikizumab pharmacokinetics to a clinically significant degree. The pharmacokinetics of mirikizumab in patients with severe renal impairment or any degree of hepatic impairment have not been evaluated.[1]

Table 1: Available pharmacokinetic parameters for mirikizumab[1]

	Mirikizumab 300mg IV	Mirikizumab 200mg SQ
Absorption	Cmax = 99.7mcg/mL	Cmax = 10.1mcg/mL Tmax = 5 days (median) F = 44%
Distribution	4.83 L	
Metabolism	Degraded into small peptides and amino acids via catabolic pathways	
Excretion	$t_{½}$ = 9.3 days	

Standard of Care/Clinical Guidelines:

The American Gastroenterological Association (AGA) published clinical practice guidelines on the management of moderate to severe UC in 2020. Recommendations related to adult outpatients follow:[2]

Induction of remission

- Infliximab and vedolizumab are suggested over adalimumab in patients naïve to biologic therapy (conditional recommendation, moderate quality of evidence).
- Ustekinumab or tofacitinib should be considered over vedolizumab or adalimumab in patients previously exposed to infliximab, especially those with a lack of response (conditional recommendation, low quality of evidence).
- Monotherapy with a TNF-alpha antagonist, vedolizumab, ustekinumab, or tofacitinib is recommended over thiopurine monotherapy (conditional recommendation, low quality of evidence).
- Thiopurine monotherapy is not recommended (conditional recommendation, very low quality of evidence).
- Methotrexate monotherapy is not recommended (conditional recommendation, low quality of evidence).

Maintenance of remission

- Thiopurine monotherapy is recommended over no treatment (conditional recommendation, low quality of evidence).
- No recommendation for or against monotherapy with a biologic agent or tofacitinib over thiopurine monotherapy (knowledge gap).
- Methotrexate monotherapy is not recommended (conditional recommendation, low quality of evidence).

Combination therapy

- Combining a TNF-alpha antagonist, vedolizumab, or ustekinumab with thiopurines or methotrexate is recommended over biologic monotherapy (conditional recommendation, low quality of evidence).
- Combining a TNF-alpha antagonist, vedolizumab, or ustekinumab with thiopurines or methotrexate is recommended over thiopurine monotherapy (conditional recommendation, low quality of evidence).

Mirikizumab was not approved at the time of guideline development; therefore, its place in therapy is unclear.

Comparative Clinical Efficacy:

Mirikizumab was approved on the basis of two double-blind, placebo-controlled, Phase III clinical trials in nearly 1200 patients with moderately or severely active UC. The first trial (LUCENT-1) was a 12-week induction study evaluating mirikizumab 300mg administered via intravenous infusion every 4 weeks. The second trial (LUCENT-2) was a 40-week maintenance study evaluating mirikizumab 200mg administered via subcutaneous injection every 4 weeks. Patients enrolled in the maintenance trial were those that had achieved clinical response in LUCENT-1. All patients enrolled had previously experienced inadequate response, loss of response, or intolerance to at least one approved UC therapy. The primary endpoint was clinical remission, which was based on the modified Mayo score (MMS). The MMS includes assessments for stool frequency, rectal bleeding, and endoscopic findings. Each of the three assessments is rated from 0 (none) to 3 (most severe), with a range of 0-9 for the total MMS. To be enrolled in the study patients required an MMS of 4-9. Clinical remission was reached if a patient achieved a stool frequency subscore of 0 or 1 (with at least a 1-point decrease from baseline), rectal bleeding subscore of 0, and an endoscopic subscore of 1 or less.[3]

After induction therapy, the rate of clinical remission was around 24% and 13% with mirikizumab and placebo, respectively. For every 10 patients treated with mirikizumab over placebo, one additional patient experienced clinical remission at 12 weeks. Rates of clinical remission after 52 weeks of therapy (12 weeks induction, 40 weeks maintenance therapy) in those that achieved clinical response after the induction phase were around 50% and 25% with mirikizumab and placebo, respectively. For every 5 patients treated with mirikizumab over placebo, one additional patient experienced clinical remission at 52 weeks. Mirikizumab also significantly improved the proportion of patients achieving glucocorticoid-free clinical remission, endoscopic remission, and histologic-endoscopic mucosal remission after 40 weeks of maintenance therapy.[3]

Adverse Reactions:
Mirikizumab was generally well-tolerated across the two trials described in Table 2. In the induction trial, upper respiratory tract infections were reported in 8% of patients treated with mirikizumab compared with 6% of patients treated with placebo. The most common adverse effects reported in the maintenance trial are described in Table 3 below. Rates of infections, serious infections, and hepatic enzyme elevations were similar between mirikizumab and placebo in both the induction and maintenance trials.[1]

Table 2: Adverse reactions reported in at least 2% of patients and at a higher rate than placebo.[1]

	Mirikizumab 200mg SQ (n = 389)	Placebo (n = 192)
Arthralgia	7%	4%
Headache	4%	1%
Herpes Viral Infection	2%	1%
Injection Site Reactions	9%	4%
Rash	4%	1%
Upper Respiratory Tract Infection	14%	12%

Boxed Warning:
Mirikizumab does not carry a Boxed Warning.[1]

QT Prolongation:
The label for mirikizumab does not address its effect on cardiac electrophysiology.[1] No evidence addressing mirikizumab's effect on the QTc interval was identified.

Contraindications, Warnings & Precautions:
Because mirikizumab may increase the risk of infection, it should not be initiated in patients with clinically important active infections. The risks and benefits of mirikizumab should be considered before initiating therapy in patients with chronic infections or history of recurrent infections. Patients should be evaluated for tuberculosis before initiating mirikizumab. One case of drug-induced liver injury has been reported in a patient using mirikizumab, although the length of induction therapy was longer than recommended. Liver enzymes should be monitored, and treatment should be interrupted if liver injury is suspected. Treatment options other than mirikizumab should be considered in patients with liver cirrhosis.[1]

Drug Interactions:
No clinically relevant drug interactions have been identified with mirikizumab. However, the use of live vaccines should be avoided in patients taking mirikizumab due to the potential for an increased risk of infection.[1,4]

Recommended Monitoring:
Liver enzymes and bilirubin should be evaluated at baseline and for at least the first 24 weeks of treatment. Patients should also be monitored for signs and symptoms of infection, including active tuberculosis.[1]

Geriatric/Nursing Considerations:
In the phase III clinical trials for mirikizumab, 8% and 1% of patients were aged ≥65 years and ≥75 years, respectively. However, given the small overall number of patients 65 years of age and older, researchers were not able to determine if older patients respond differently to mirikizumab when compared with younger patients. Pharmacokinetic parameters are similar between older and younger adult patients.[1]

Dosing and Availability:
Mirikizumab is available as a 300mg/15 mL solution in a single-dose vial for intravenous infusion. It is also available as a 100mg/mL solution in a single-dose prefilled pen for subcutaneous injection.[1]

Usual Adult Dosage**:**

- Induction: 300mg via intravenous infusion over at least 30 minutes at week 0, week 4, and week 8
- Maintenance: 200mg via subcutaneous injection, given as two consecutive 100mg injections at week 12 and every 4 weeks thereafter

Renal Dosing: No dosing recommendations provided.

Hepatic Dosing: No dosing recommendations provided.

Geriatric Dosing: See Adult Dosing

Summary:

1. Mirikizumab is an IL-23 antagonist FDA-approved for the treatment of adults with moderately to severely active UC.
2. In clinical research, mirikizumab significantly increased the proportion of patients achieving clinical remission at both 12 weeks and 52 weeks when compared with placebo.
3. Mirikizumab does not carry a Boxed Warning or concern for clinically relevant drug interactions; however, its use should be avoided alongside live vaccines.
4. Mirikizumab may increase the risk of infections, and its initiation should be avoided in patients with clinically important active infections.
5. Hepatotoxicity has been reported with mirikizumab, and liver enzymes should be monitored throughout therapy.
6. Induction therapy with mirikizumab involves an intravenous infusion every 4 weeks for a total of 3 infusions. Maintenance therapy with mirikizumab involves subcutaneous injections every 4 weeks after completion of the induction phase.
7. It is unclear if the dose or frequency of mirikizumab should be altered in patients with renal or hepatic impairment.

References:

1. Omvoh [package insert]. Indianapolis, IN; Eli Lilly and Company; October 2023.
2. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. *Gastroenterology*. 2020;158(5):1450-1461.
3. D'Haens G, Dubinsky M, Kobayashi T, et al. Mirikizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2023;388(26):2444-2455.
4. Mirikizumab. Clinical Pharmacology. Tampa, FL: Elsevier/Gold Standard; 2024. https://www.clinicalkey.com/pharmacology/monograph/5496 [subscription required]. Accessed March 10, 2024. Updated October 30, 2023.