De Novo Inflammatory Bowel Disease in Patients on IL-1 Inhibitor Therapy For Rheumatologic Diseases

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Introduction:

- Interleukin-1 inhibitors are immunosuppressive drugs that target the proinflammatory cytokines IL-1α and IL-1beta.
- IL-1 inhibitors can be used to treat various rheumatologic disorders
- The three available IL-1 inhibitors are anakinra, canakinumab and rilonacept
- Although there are a few reports implicating IL-1 inhibitors as causes of inflammatory bowel disease (IBD), this is not a well-established adverse effect
- The FDA Adverse Event Reporting System (FAERS) is a publicly available database for post-marketing surveillance of drug safety

Objectives:

- Evaluate FAERS reports to examine the possible relationship between incidence of de novo IBD and treatment with IL-1 inhibitor therapies for various rheumatologic conditions

Methods:

- All FAERs reports for patients receiving anakinra, canakinumab or rilonacept were investigated
- Only “primary suspect” reports of IBD as an adverse event were selected
- Subsequently, files were queried for inflammatory bowel disease, Crohn’s disease and ulcerative colitis as reaction terms
- Detailed reports of these cases were requested from the FDA
- The Adverse Drug Reaction Probability Score, (Naranjo Scale), was applied to each case to assess the likelihood of a causal relationship between the IL-1 inhibitor and the adverse effect of de novo IBD (see Table 1)
- The probability of the drug reaction is assigned via a score for a definite (≥9), probable (5-8), possible (1-4) or doubtful (≤0) reaction

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Table 1. The Adverse Drug Reaction Probability Scale, also known as the Naranjo scale. Cumulative scores were interpreted as definite (≥9), probable (5-8), possible (1-4), or doubtful (≤0).

Patient Number	IL-1 Inhibitor Treatment	IBD Diagnosis	Naranjo Score	Interpretation of Score
1	Anakinra	CD	2	Possible
2	Anakinra	UC	-1	Doubtful
3	Anakinra	UC	2	Possible
4	Anakinra	CD	4	Possible
5	Anakinra	CD	2	Possible
6	Anakinra	CD	3	Possible
7	Anakinra	CD	2	Possible
8	Anakinra	CD	3	Possible
9	Anakinra	CD	4	Possible
10	Anakinra	CD	4	Possible
11	Anakinra	UC	4	Possible
12	Canakinumab	CD	5	Probable
13	Canakinumab	CD	2	Possible
14	Canakinumab	CD	2	Possible
15	Canakinumab	UC	2	Possible
16	Canakinumab	CD	3	Possible
17	Canakinumab	CD	2	Possible
18	Canakinumab	Unspecified	2	Possible
19	Canakinumab	CD	4	Possible
20	Canakinumab	Unspecified	2	Possible
21	Canakinumab	CD	4	Possible
22	Canakinumab	CD	3	Possible
23	Canakinumab	UC	2	Possible
24	Canakinumab	CD	3	Possible
25	Canakinumab	UC	4	Possible
26	Canakinumab	Unspecified	2	Possible
27	Canakinumab	CD	2	Possible
28	Canakinumab	CD	3	Possible
29	Canakinumab	CD	4	Possible

Table 2. Results of Naranjo Score by Individual Report to FAERS

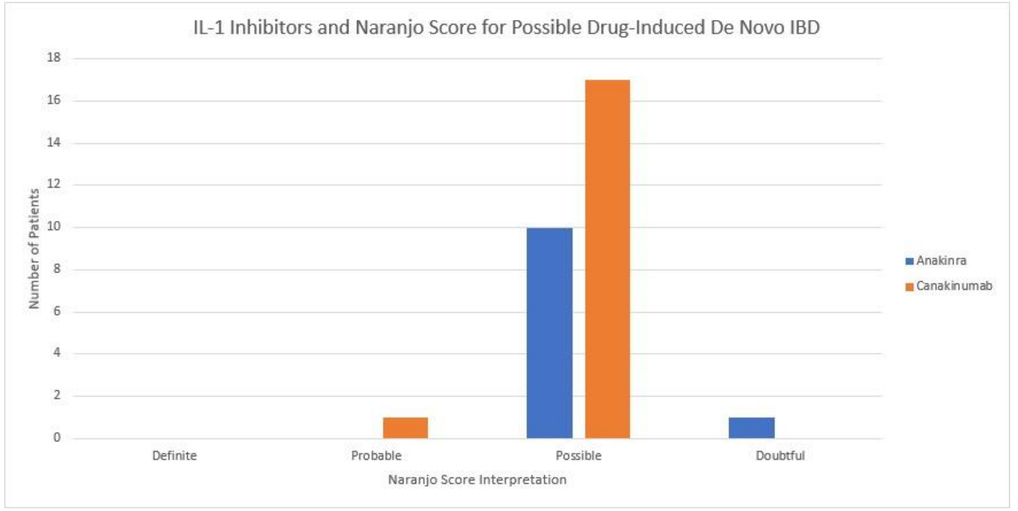

Figure 1. IL-1 Inhibitors and Naranjo Score for Possible Drug-Induced De Novo IBD. Anakinra and canakinumab are represented by blue and orange bars, respectively.

Results:

- Of the 34 cases of IBD reported in patients from IL-1 inhibitor therapy, 6 were excluded because patients had a prior history of IBD
- There were 12 reports of IBD from anakinra. Based on the Naranjo scale, 11 were possible anakinra-induced IBD and 1 was a doubtful case.
- There were 18 reports of canakinumab-induced IBD. Based on the Naranjo scale 17 were possible canakinumab-induced IBD and one was a probable case.
- There were no reports linking rilonacept therapy to IBD in the FAERs database (Table 2, Figure 1)

Conclusions:

- Review of the collected FAERS reports suggests a possible causal relationship between treatment with IL-1 inhibitors and de novo IBD
- These results are significant, as the underlying pharmacodynamics of these medications may either unmask or initiate IBD in these patient populations being treated for various rheumatologic disorders
- Further investigation of the mechanisms driving the development of IBD in patients on IL-1 inhibitor therapy is needed.