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Efficacy of Canakinumab vs. triamcinolone acetonide according to multiple gouty arthritis-related health outcomes measures

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SUMMARY

Aim: Canakinumab (CAN), a selective, fully human, anti-IL-1β monoclonal antibody, has demonstrated long-term benefits in gouty arthritis (GA) patients, who have contraindications for, or are unresponsive or intolerant of, non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine (two trials:β-RELIEVED [$n = 228$]; β-RELIEVED II [$n = 226$]). The trials collected different responses, including patient-reported outcomes (PRO). A composite response end-point (CRE) was used to interpret each patient's overall response to treatment. **Methods:** Data from β-RELIEVED trials were pooled for this retrospective analysis. The CRE representing overall change in GA-related health outcomes, from baseline to 12 weeks, included clinical markers; PROs from the Gout Impact Scale (GIS); and the SF-36 bodily pain scale. Response to each variable (i.e. markedly important difference) was determined *a priori*. Variable values [1 (responder) or 0 (non-responder)] were summed to create a CRE score for each patient. **Results:** For eight of 12 variables measured, the percentage of CAN responders was significantly greater than for TA ($p < 0.05$). On average, patients receiving CAN met a higher percentage of response criteria (65%) than patients receiving triamcinolone acetonide (TA) (49%), $p < 0.001$. Mean CRE scores were significantly higher for CAN vs. TA (mean [SD]; 4.7 [2.7] vs. 3.7 [2.4], $p < 0.001$). Treatment differences remained even after serially removing individual responder variables and domains from the composite end-point, indicating that the differences between CAN and TA were robust. **Conclusion:** CAN was superior to TA across multiple health-outcome variables comprising clinical markers and PRO over 12 weeks in patients contraindicated, intolerant or unresponsive to NSAIDs and/or colchicine.

What's known

Gouty arthritis patients often experience frequent flares, persistent pain, and impaired physical functioning that have a major impact on the patient's health-related quality of life. The efficacy and safety of canakinumab has been previously demonstrated using univariate analyses of individual treatment response measures (e.g. pain scores, time to first new flare) in two 12-week, multicenter, double-blind, double-dummy, active-controlled clinical trials (b-RELIEVED and b-RELIEVED II).

What's new

This study used a novel composite score approach to interpret clinical trial results more from the patient's perspective, allowing varied patient-specific patterns of response across multiple variables, including health-related quality of life, to be counted as treatment success. Using a single composite outcomes response index revealed patients in the Canakinumab group were significantly more likely to meet multiple responder criteria, suggesting a global, multidimensional effect of Canakinumab compared to Triamcinolone Acetonide.

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Introduction

Gouty arthritis (GA) is caused by the deposition of monosodium urate crystals in joints, which induces release of interleukin-1β (IL-1β) that mediates inflammatory responses (1–3). GA patients often experience frequent flares, persistent pain and impaired physical functioning which have a major impact on the patient's health-related quality of life (HRQoL) (4,5). Current treatment options to manage pain and inflammation associated with acute flares include anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine; however, some patients have contraindications for, or are unresponsive or intolerant to, these drugs (6).

Canakinumab (CAN), a selective, fully human, anti-IL-1β monoclonal antibody has been approved in the European Union for the symptomatic treatment of adult patients with difficult to treat gouty arthritis defined as at least three attacks in the previous 12 months, contraindicated/intolerant/inadequate responders to NSAIDS and Colchicine and in whom repeated courses of corticosteroids are not appropriate. In several other countries including Russia and Philippines, it is indicated for the use in a less restricted population similar to the one described in the present analysis.

The efficacy and safety of CAN was previously demonstrated in two 12-week, multicenter, double-blind, double-dummy, active-controlled trials (β-RELIEVED and β-RELIEVED II) (7). The trials included measurement of many different outcome measures such as the number of flares over time, as well as patient-reported outcome (PRO) questionnaires related to HRQoL.

However, missing values were encountered among some of the PRO data because of two main reasons. Firstly, because of the unavailability of culturally adapted versions of questionnaires not all patients completed all the questionnaires. Secondly, patients completed specific questionnaires, and not others, depending on the primary location of their GA flares (i.e. upper or lower extremities). Given that the trial had multiple outcome measures, each having varying degrees of sensitivity, and the systematic missing data for PROs, a composite outcomes response end-point was considered the best option for interpreting each patient's overall response to treatment.

The purpose of this analysis was to assess the overall change in GA-related health outcomes experienced by patients during 12 weeks of CAN vs. triamcinolone acetonide (TA) therapy using a composite health outcomes response end-point.

Patients and methods

Study design

Pooled data from the two clinical trials of the β-RELIEVED program were used for this retrospective analysis. "Data from the identical phase three trials were pooled in order to increase the sample size (thus avoiding Type II statistical error) and to increase the generalisability of the results." The trials included patients meeting the ACR 1977 preliminary criteria for acute GA and contraindicated, intolerant or unresponsive to NSAIDs and/or colchicine. Both core studies (two trials: β-RELIEVED [$n = 228$]; β-RELIEVED II [$N = 226$]) were 12-week, multiregional, active-controlled, double-blind, parallel-group, double-dummy and phase 3 studies (7). Patients were assigned to receive either a single dose CAN 150 mg s.c. or TA 40 mg i.m. to treat an acute GA attack and were redosed "on demand" on each new attack. A composite response end-point (CRE) representing overall change in GA-related health outcomes (clinical markers and patient-reported outcomes) from baseline to 12 weeks was used to examine each patient's overall response to treatment.

Composite response end-point

Multiple outcomes for each patient were consolidated into a CRE to capture a more comprehensive picture of overall response to treatment. This consolidated approach also allowed inclusion of outcomes variables with systematic missing data and protected against type 1 error (false positive) that could result from conducting multiple univariate tests. Variables included in the CRE reflected the clinical dimensions suggested by expert rheumatologists (8). The CRE representing overall change in GA-related health outcomes, from baseline to 12 weeks, included clinical markers (serum urate, flare activity and use of rescue medications to treat flares); patient-reported outcomes data from the Gout Impact Scale (GIS) of the Gout Assessment Questionnaire 2.0 (9); five questions related to overall experience of gout (gout pain, well-being, gout-related quality of life, and gout-related physical and mental health); and the SF-36 bodily pain scale. The criteria used as the responder definition (i.e. markedly important difference) for each variable was determined *a priori* based on published research and/or expert opinion (10–12). Details of the content, derivation and psychometric properties, including good internal reliability across age, race and gender (Cronbach's alpha 0.66–0.80), of the CRE have been presented elsewhere (13).

Procedure

Scoring for each of the 12 outcome variables was transformed into a common metric (i.e. responder yes or no) using the *a priori* responder definitions and clinically meaningful cut-offs. Patients were categorised as responders for each variable if they had greater than a minimally important change from baseline to 12 weeks. Finally, variable values [1 (responder) or 0 (non-responder)] were summed to create a CRE score for each patient (possible range 0–12). A total CRE score was calculated as the percentage of response criteria met out of the total number of response criteria.

Analyses

Chi-square analysis was used to test differences in proportion of responders for each variable and then the average percentage of responder criteria met per subject between treatment groups. Analyses assumed missing values were non-responders; treatment groups were not different in the number of missing responder data points ($p = 0.55$). An independent samples *t*-test was used to compare CRE scores (i.e. average number of responder variables achieved) between treatment groups. The Institutional Review Board of University of California, San Diego approved the study.

Results

There was no significant difference in the demographical and clinical profile between the CAN vs. TA group; the majority of patients were male (89.3% vs. 93.0%), Caucasian (74.2% vs. 76.9%), mean age of 52.3 (SD 11.8) vs. 53.6 (SD 11.5) and mean number of GA flares in past year 6.5 (SD 5.6) vs. 6.5 (SD 4.8), respectively. Common comorbidities in the CAN vs. TA group were hypertension (58.2% vs.

60.7%), obesity (52.0% vs. 53.7%), dyslipidemia (38.2% vs. 44.5%) and metabolic syndrome (35.6% vs. 28.8%). There was no significant difference in proportion of patients using urate-lowering therapy (39.6% vs. 45.0%) or for whom NSAIDS and/or colchicine were contraindicated (39.0% vs. 32.0%) between the CAN and TA groups.

For eight of 12 variables measured, the percentage of CAN responders was significantly greater than that for TA, $p < 0.05$ (Table 1). The percentage of responders did not differ significantly between groups for four variables; change in serum urate, SF-36 bodily pain scale, general well-being and gout-related physical health. On average, patients receiving CAN met a higher percentage of response criteria (65%) than patients receiving TA (49%), $p < 0.001$ (Table 1). Patients in the CAN group were significantly more likely ($p < 0.05$) to meet a higher percentage of responder criteria at any level above 20% of criteria met (Figure 1). The mean CRE score was significantly higher for CAN patients vs. TA patients (mean $\pm$ SD; 4.7 ± 2.7 vs. 3.7 ± 2.4, $p < 0.001$; Table 2). No single variable in the CRE score appeared to drive between-group differences since scoring significance between groups did not change when individual variables were removed (Table 2). In addition, no single domain within the CRE was responsible for between-group differences since scoring between group differences remained significant when individual domains were removed.

Discussion

These results demonstrate superior efficacy, across multiple health-outcome variables comprising clinical markers and PROs, of CAN vs. TA over 12 weeks in patients contraindicated, intolerant or unresponsive to NSAIDS and/or colchicine. Our findings are consistent with a pooled data review that found CAN patients had lower mean pain scores, time to first new attack and reduced risk of a new GA attack at 12 weeks. (12) In this study, we were also able to include patient-reported HRQoL variables and found consistent significant differences in percentage of patients reaching responder level that favoured CAN. Specifically, patients in the CAN group were significantly less likely to report having a flare and to use rescue medication during the study period. CAN patients were also more likely to expe-

Table 1 Responders (%) for gouty arthritis-related health outcomes measures at 12 weeks

Outcome domain	Item no.	Variable	Responder definition	Canakinumab (%)	TA (%)
Urate	1	Serum urate	> 25% reduction	6.5% *n* = 199	8.8% *n* = 204
Flare frequency	2	Flare past 4 weeks	No	90.2%*** *n* = 112	68.1% *n* = 113
	3	New flare during trial	No	71.6%*** *n* = 225	51.1% *n* = 229
	4	Use of rescue medications during trial	No	58.7%*** *n* = 225	38.4% *n* = 229
Pain	5	Gout pain severity past 4 weeks (GIS, 1–10 scale)	> 2 point reduction	85.0%* *n* = 113	74.3% *n* = 113
	6	Bodily pain (SF-36, 0–100 scale)	> 10 point reduction	66.1% *n* = 192	58.6% *n* = 181
Patient global response	7	How well doing past 4 weeks (GIS, 1–10 scale)	> 2 point reduction	69.0% *n* = 113	58.4% *n* = 113
	8	Global treatment response	Acceptable, good, or excellent	94.3%** *n* = 211	85.4% *n* = 213
	9	GIS-Global Control Scale (GIS, 0–100)	> 8 points	81.4%* *n* = 113	70.2% *n* = 114
HRQoL (Disease specific)	10	Gout-related quality of life	> 1 point improvement	41.5%** *n* = 65	18.8% *n* = 85
	11	Gout-related physical health	> 1 point improvement	31.1%** *n* = 61	19.5% *n* = 82
(GIS, very poor – excellent)	12	Gout-related mental health	> 1 point improvement	30.6%** *n* = 62	10.4% *n* = 77
Average Percentage Responder Criteria met (considering number of variables measured)				65.0%***	49.0%

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$. HRQoL, health-related quality of life; GIS, Gout Impact Scale.

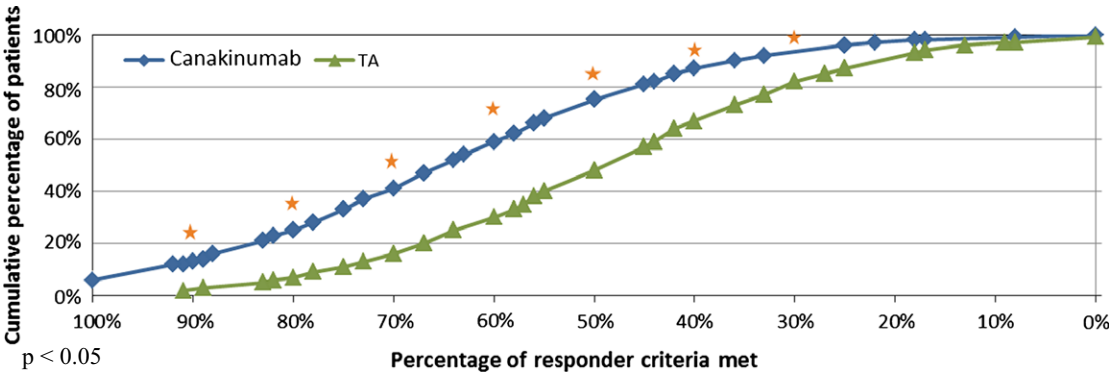

Figure 1 Expected cumulative percentage of patients meeting response criteria (Baseline vs. Day 85) (considering number of variables measured per patient). $p < 0.05$

Table 2 Mean composite responder end-point score removing each item*†

Variable removed	Canakinumab *N* = 225	TA *N* = 229
Overall Composite Responder Score – No Variables Removed	4.7 (2.7)***	3.8 (2.4)
25% Reduction In Uric Acid	4.7 (2.7)***	3.7 (2.4)
Patient Reported No Gout Flare In Past 4 Weeks	4.3 (2.4)***	3.4 (2.1)
No New Gout Flare During Clinical Trial	4.0 (2.3)***	3.2 (2.3)
Patient Did Not Take Rescue Medication During Clinical Trial	4.1 (2.6)***	3.4 (2.3)
Marked Improvement in Pain Severity Item	4.3 (2.3)***	3.4 (2.1)
Marked Improvement in Bodily Pain Scale Item	4.2 (2.5)***	3.3 (2.2)
Marked Improvement in How Well Doing Item	4.4 (2.4)***	3.5 (2.1)
Patient-Reported Acceptable, Good, or Excellent Treatment Response	3.8 (2.6)***	2.9 (2.2)
Marked Improvement in GIS-Global Scale	4.3 (2.7)***	3.4 (2.9)
Marked Improvement in Gout-Related Quality of Life	4.6 (2.5)***	3.7 (2.3)
Marked Improvement in Gout-Related Mental Health	4.6 (2.6)***	3.7 (2.3)
Marked Improvement in Gout-Related Physical Health	4.6 (2.3)***	3.7 (2.3)
All Flare items	3.2 (2.0) **	2.6 (1.9)
All Pain items	3.7 (2.1) ***	2.9 (1.8)
All Patient Global Response items	3.1 (1.9) ***	2.3 (1.6)
All Gout-Related Quality of Life items	4.4 (2.3) ***	3.6 (2.1)

*Mean number of responder variables out of 12. †All patients; missing values are assumed as non-responders; no significant difference in number of responder data points between groups ($p = 0.55$). ***$p < .001$; **$p < 0.01$. GIS, Gout Impact Scale.

rience a marked reduction in gout-related pain, report favourable response to treatment, marked improvement on overall GA control and improved GA-related quality of life outcomes (overall and mental health).

Using the single composite outcomes response index revealed patients in the CAN group were significantly more likely to meet multiple responder criteria, suggesting a global, multidimensional effect of CAN compared with TA. Moreover, sensitivity analyses indicated the group differences were not because of any single responder criterion. Treatment differences between CAN and TA remained even after serially removing individual responder variables and domains from the composite end-point, indicating that the differences between CAN and TA were robust. Use of the CRE score allowed capture of global response to treatment despite variation among patients. For example, by using a CRE score, patients responding to five of 12 responder variables, regardless of which five variables, were viewed as equivalent responders. The composite score approach allows interpretation of study results more from the patient's perspective since it allows patient response to outcomes variables in various patient-specific patterns to be counted as treatment success, rather than requiring prescribed cut-offs for specific univariate analyses.

Limitations

The data used for our retrospective analyses were for the 12-week period of two clinical trials conducted in a limited population. Results may differ for other populations and over longer time periods of treatment or with differing doses of TA. The CRE in this retrospective analysis was limited to the health outcomes that were collected in the clinical trials and missing values for some PRO data are a limitation to this analysis. Results may have differed if, for example, all patients (instead of only those with GA attacks in lower extremities) had completed the SF-36. We only included gout-specific measures in our CRE, with the exception of the SF-36 bodily pain scale that was included since pain is a dominant feature of gout and the questions in this scale are specific to pain. While scores for the HAQ-DI and EQ-5D were available for some patients in the trials, they were not included because of their non-gout specific focus. No single variable in the CRE score appeared to drive differences between groups; however, it should be noted that some elements of the CRE scale were correlated with each other as they reflected related aspects of outcomes. Although the outcomes available for analysis represented most of those suggested by expert rheumatologists (8), presence of tophi was not consistently available in the clinical trial data and there may be other variables that are important to patients in defining successful response to treatment.

Conclusion

The results of this study support the superior efficacy of canakinumab vs. triamcinolone acetonide across multiple GA-related health outcome measures during a 12-week trial in patients contraindicated, intolerant or unresponsive to NSAIDS and/or colchicine. Interpretation of study results from an overall patient perspective, using a composite outcomes response end-point, revealed canakinumab patients were significantly more likely to meet multiple responder criteria, including number of flares, patient-reported symptom severity, functioning and HRQoL.

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Author contributions

Jan D. Hirsch, BS Pharm, PhD: concept/design, results interpretation, drafting and revising article, approval of article, funding secured. Ari Gnanasakthy, MSc, MBA: concept/design, results interpretation, drafting and revising article, approval of article. Rachel Lale, MA: statistical analysis, results interpretation, drafting and revising article, approval of article. Kyle Choi, MPH: statistical analysis, results interpretation, drafting and revising article, approval of article. Andrew J. Sarkin, PhD: concept/design, statistical analysis, results interpretation, drafting and revising article, approval of article.

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