

# Usability and Patient Perceptions of the Sarilumab Pen for Treatment of RA

Kivitz A, Baret-Cormel L, van Hoogstraten H, et al. Usability and patient preference phase 3 study of the sarilumab pen in patients with active moderate-to-severe rheumatoid arthritis. *Rheumatol Ther* 2018;5:231–42.

## Study Overview

**Objective.** To assess usability and patient perceptions of the sarilumab auto-injector device (“sarilumab pen”) among patients with moderate-to-severe rheumatoid arthritis (RA).

**Design.** 12-week, randomized, parallel-group usability study.

**Setting and participants.** The study was conducted at 53 centers in 6 countries. Inclusion criteria were a diagnosis of RA (as defined by American College of Rheumatology/ European League Against Rheumatism 2010 Criteria) of  $\geq 3$ -month disease duration, willing and able to self inject, continuous treatment with 1 or a combination of nonbiologic disease modifying antirheumatic drugs (except leflunomide in combination with methotrexate); and moderately to severely active RA, defined as 4/66 swollen joint, 4/68 tender joints, and high-sensitivity C-reactive protein (hsCRP) measurement  $\geq 4$  mg/L. Exclusion criteria were age  $< 18$  years, prior treatment with anti-interleukin 6 (IL-6) or IL-6 receptor (IL-6R) antagonists; treatment with tumor necrosis factor (TNF) antagonists; treatment with RA-directed biologic agents other than with a TNF- $\alpha$

antagonist mechanism as follows: anakinra, abatacept, rituximab or other cell-depleting agent; and prior treatment with a Janus kinase inhibitor.

Patients were randomized 1:1:1:1 to sarilumab 150 or 200 mg every 2 weeks administered by single-use, disposable, prefilled pen or pre-filled syringe. Randomization method was not reported.

**Main outcomes measures.** The primary endpoint was number of “product technical failures” (PTFs). Patients randomized to the pen were given a diary that had questions related to their ability to remove the cap, start the injection, and complete the injection. Participants were asked to answer the questions each time they used the pen. If the response was “no” to any of the 3 questions, this was considered a “product technical complaint” (PTC). PTCs that had a validated technical cause based on pen evaluation and analysis were considered PTFs.

In addition, patient perceptions and satisfaction with the pen were assessed via questionnaire. At baseline, patients were asked about injections and prior experience with self-injection, and at 12 weeks they were asked about their experiences in using the pen. Other outcomes assessed included adverse events and pharmacokinetic parameters.

## Outcomes Research in Review SECTION EDITORS

### KRISTINA LEWIS, MD, MPH

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Mount Sinai School of Medicine  
New York, NY

### KATRINA F. MATEO, MPH

CUNY School of Public Health  
New York, NY

### DANIEL ISAAC, DO, MS

Michigan State University  
East Lansing, MI

**Results.** 217 participants were enrolled: 108 patients were in the pen group (56 randomized to 150 mg and 52 randomized to 200 mg) and 109 were in the syringe group (53 randomized to 150 mg and 56 randomized to 200 mg). Completion rates were similar among groups. Sixteen patients discontinued due to treatment-emergent adverse events. There were no PTFs. There was one PTC, in which the user accidentally bumped the pen, which expelled the drug onto the floor.

At baseline, before the first injection, the majority of patients reported that they were not afraid of needles (58%), had past experience with self-injections (55%), and were either “very confident” or “extremely confident” regarding self-injections (55%). After the 12-week assessment phase, when asked about their overall level of satisfaction, 98% of patients reported they were “satisfied” or “very satisfied” with the sarilumab pen.

Treatment emergent adverse events occurred in 66% of patients, with no clinically meaningful differences leading to discontinuation in the pen and syringe groups. The most common adverse events were infections and neutropenia.

**Conclusion.** Patients successfully completed self-injections with the sarilumab pen and found it easy to use.

### Commentary

Rheumatoid arthritis (RA) is a common immune-mediated disease characterized by chronically progressive inflammation and destruction of joints and associated structures, resulting in significant morbidity, mortality, and disability. Improved understanding of RA disease pathogenesis in recent years has led to the development of new biologic treatments designed to target specific elements of the RA inflammatory response.

Sarilumab is an interleukin-6 blocker that was approved in the US in 2017 for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs. While a syringe form of this drug is currently available, at the time

of this writing the pen has not yet been released.

In this real-world usability study sponsored by Sanofi, there were no technical difficulties with using the pen. Most patients thought the pen was easy or very easy to use, and safety and efficacy appeared to be generally comparable between the pen and syringe. The pen also offers safety protection features that prevent needlestick injury.

The authors of the current study noted that results from previous studies have shown that patients with RA favor treatment devices that are easy to use, convenient, less painful, and take less time to use, and patients have demonstrated a preference for autoinjector devices over more conventional methods of treatment administration [1–3], such as syringes. Pens have been well accepted for the treatment of other chronic health conditions, including diabetes mellitus, migraine headaches, and growth hormone deficiency, and subcutaneous administration of a tumor necrosis factor (TNF) inhibitor via pen has also been accepted for the treatment of RA [1]. As RA requires lifelong treatment, the use of a pen that is ergonomically designed to take into account the manual dexterity issues relevant to this patient population could potentially enhance compliance.

### Applications for Clinical Practice

A prefilled pen was well accepted and associated with favorable patient perceptions, indicating that this delivery system may be a viable option for RA patients who are prescribed sarilumab.

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# Are There Differences in Efficacy and Safety Between 2nd-Generation Drug-Eluting Stents for Left Main Coronary Intervention?

Lee PH, Kwon O, Ahn JM, et al. Safety and effectiveness of second-generation drug-eluting stents in patients with left main coronary artery disease. *J Am Coll Cardiol* 2018;71:832–41.

## Study Overview

**Objective.** To compare the effectiveness and safety profiles of various second-generation drug-eluting stents (DES) for left main coronary intervention.

**Design.** Retrospective study using 3 multicenter prospective registries (IRIS-DES, IRIS-MAIN, PRECOMBAT).

**Setting and participants.** Among the 4470 patients enrolled in the 3 registries treated between July 2007 and July 2015, the authors identified 2692 patients with significant left main coronary artery disease who received second-generation DES for inclusion in the study. The centers for IRIS-DES and PRECOMBAT are academic and community hospitals in South Korea, with IRIS-MAIN involving academic and community hospitals in South Korea, China, India, Indonesia, Japan, Malaysia, Taiwan, and Thailand. Of the patients in these registries, 1254 received cobalt-chromium everolimus-eluting stents (CoCr-EES), 232 biodegradable polymer biolimus-eluting stents (BP-BES), 616 platinum-chromium EES (PtCr-EES) and 590 Resolute zotarolimus-eluting stents (Re-ZES).

**Main outcome measure.** Target-vessel failure.

**Main results.** At 3 years, rates of target-vessel failure were not significantly different for the different types of stents (16.7% for the CoCr-EES, 13.2% for the BP-BES, 18.7% for the PtCr-EES, and 14.7% for the Re-ZES;  $P = 0.15$ ). The adjusted hazard ratios (HRs) for target-vessel failure were similar in between-group comparisons of the different stents, except for the PtCr-EES versus the BP-BES (HR 1.60, 95% confidence interval 1.01 to 2.54;  $P = 0.046$ ). There were no significant differences in risk of

composite of all-cause death, any myocardial infarction, or any revascularization and its individual components according to the different types of stents.

**Conclusion.** There was no significant between-group differences in 3-year risk of target-vessel failure, except for a higher risk of primary outcome with PtCr-EES compared to BP-BES.

## Commentary

Left main coronary artery disease is identified in 5% to 7% of the population and is one of the more perplexing lesions to treat given the poorer outcome compared to non-left main lesion and the importance of the vessels the left main supplies [1]. Historically, coronary artery bypass grafting (CABG) has been the standard of care on the basis of the survival benefit observed in early trials compared with medical therapy. Left main percutaneous coronary intervention (PCI) has evolved as an alternative to CABG over the past few decades. Early studies using balloon angioplasty or bare metal stents were limited primarily due to high restenosis rate [1]. In the DES era, results have been overall comparable to CABG. Unprotected left main PCI using first-generation DES was non-inferior compared to CABG in the pre-specified sub-study of SYNTAX trial and in PRECOMBAT trial using paclitaxel-eluting stents and sirolimus-eluting stents, respectively [2,3]. Largely based on these trials, the 2014 ACC/AHA guidelines give class IIa recommendation for patients with low-risk anatomy (Syntax score 0–22) and class IIb recommendation for patients with intermediate-risk anatomy (Syntax score 23–32) for left main PCI [4]. Moreover, European guidelines give class Ib recommendation for patients with low-risk anatomy, and

class IIa recommendation for intermediate-risk anatomy for left main PCI [5]. However, the SYNTAX trial and PRECOMBAT trial were limited by not meeting non-inferiority (SYNTAX) and wide non-inferiority (PRECOMBAT) and selection bias due to large exclusion criteria. In addition, first-generation DES were used in these trials (tacrolimus-eluting stent for SYNTAX and sirolimus-eluting stent for PRECOMBAT). The standard of care has now shifted to wide use of second-generation DES [1].

Subsequently, 2 larger-scale clinical trials using second-generation DES were designed and results have been reported recently [6,7]. The EXCEL trial enrolled 1905 patients with significant left main coronary disease and compared CoCr-EES to CABG. At 3 years, the primary endpoint of a composite of death from any cause, stroke, or myocardial infarction occurred in 15.4% of the PCI patients and in 14.7% of the CABG patients ( $P = 0.02$  for non-inferiority;  $P = 0.98$  for superiority). Similarly, the NOBLE trial enrolled 1201 patients with significant left main coronary disease and compared PCI to CABG. In this trial, the biolimus-eluting second-generation stent became their preferred stent during the study period. At 5 years, the primary endpoint of a composite of all-cause mortality, non-procedural myocardial infarction, any repeat coronary intervention, and stroke was higher in PCI compared to CABG patients (28% vs 18%, HR 1.51, 95% CI 1.13–2.00), exceeding the limit of non-inferiority, and CABG was significantly better compared to PCI ( $P = 0.004$ ). The difference in the results is likely due to trial design. The primary endpoint was different in the 2 studies—EXCEL did not include repeat coronary intervention in the composite endpoint. The NOBLE study had a longer enrollment period and earlier-generation stents (sirolimus-eluting) were used in the earlier stages of the trial. In addition, the NOBLE study did not assess for peri-procedural myocardial infarction as an endpoint, which is known to be associated with adverse outcome. In both trials, cardiovascular mortality and all-cause mortality were similar at the end of follow-up.

In this context, the Lee et al study compared 4 types of currently available second-generation stents by pooling data from 3 large registries in Asia [8]. The main finding from this study was that target-vessel failure, defined as the composite of cardiac death, target-vessel

myocardial infarction, or target-vessel revascularization at 3 years follow-up was not different among the types of second-generation drug eluting stents ( $P = 0.15$ ).

Another important finding from this study was that the stent thrombosis rate at follow-up was very low ( $< 1\%$ ). This is consistent with the EXCEL study, which reported a definite stent thrombosis rate of 0.7% and was lower than in the NOBLE study, which reported a rate of 3%. One of the possible explanations for this difference could be stent selection. In contrast to the EXCEL study, which exclusively used Co-Cr EES by study protocol, NOBLE study included first-generation sirolimus-drug eluting stent (11%) and BP-BES (89%). However, there are multiple factors that contribute to stent thrombosis other than stent selection, such as lesion characteristics, adequate stent expansion, and use of dual antiplatelet therapy [9].

The observed finding of small increase in target-vessel failure in PtCr-EES versus the BP-BES needs to be interpreted with caution. First, this was an observational study, and the treatment strategy or choice of stent was determined by a local interventional cardiologist, which could lead to selection bias. Although the authors performed propensity analysis, residual confounding is likely. Second, since there was no difference in the primary analysis, the subgroup analysis becomes less important. In addition, authors did not perform statistical correction for multiple comparisons.

Despite the above limitations, this large-scale observational study gives us important insights to the performance of each second-generation DES. All currently available second-generation DES appear to be an option for use for left main coronary intervention.

### **Applications for Clinical Practice**

In patients presenting with significant left main disease, left main PCI using a contemporary second-generation stent is safe and effective and likely has equivalent outcomes to CABG. However, PCI may be associated with higher rate of repeat revascularization. The rate of target-vessel failure was similar between different types of second-generation DES.

—Taishi Hirai, MD, and John E.A. Blair, MD,  
University of Chicago Medical Center, Chicago, IL

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## Survey-Based Priming Intervention Linked to Improved Communication with the Seriously Ill

Curtis JR, Downey L, Back AL, et al. Effect of a patient and clinician communication-priming intervention on patient-reported goals-of-care discussions between patients with serious illness and clinicians - a randomized clinical trial. *JAMA Intern Med* 2018 May 26.

### Study Overview

**Objective.** To evaluate the efficacy of an intervention targeting both patients and clinicians intended to increase goals-of-care conversations.

**Design.** Multicenter cluster-randomized controlled trial.

**Setting and participants.** Clinicians (physicians or nurse practitioners) were recruited between February 2014 and November 2015 from 2 large health centers in the Pacific Northwest and were eligible if they provided primary or specialty care and had at least 5 eligible patients in their panels. Using the electronic health record (EHR) and clinic schedules, study staff identified and contacted (via mail or telephone) consecutive patients cared for by participating clinicians between March 2014 and May 2016 with the following eligibility criteria: age 18 years or older, 2 or more

visits with the clinician in the last 18 months, and 1 or more qualifying conditions. Qualifying conditions included (1) metastatic cancer or inoperable lung cancer; (2) COPD with FEV<sub>1</sub> values below 35% of that predicted or oxygen dependence, restrictive lung disease with a total lung capacity below 50% of that predicted, or cystic fibrosis with FEV<sub>1</sub> below 30% of that predicted; (3) New York Heart Association class III or IV heart failure, pulmonary arterial hypertension, or left ventricular assist device or implantable cardioverter defibrillator implant; 4) cirrhosis or end-stage liver disease; (5) dialysis-dependent renal failure and diabetes; (6) age 75 or older with one or more life-limiting chronic illness; (7) age 90 or older; (8) hospitalization in the last 18 months with a life-limiting illness; (9) Charlson comorbidity index of 6 or higher. The qualifying criteria were selected to identify a median survival of approximately 2 years, suggesting relevance of goals-of-care discussions.

**Intervention.** The intervention was the patient-specific Jumpstart-Tips intervention, intended to prime clinicians and patients for a brief discussion of goals of care during a routine clinic visit. Patients in the intervention group received a survey to assess their preferences, barriers and facilitators for communication about end-of-life care. Survey responses were used to (1) generate an abstracted version of the patient's preferences, (2) identify the most important communication barrier or facilitator, and (3) provide communication tips based on curricular materials from VitalTalk (<http://vitaltalk.org>) tailored to patient responses. The 1-page communication guide, called Jumpstart-Tips, was sent to clinicians 1 or 2 days prior to the target clinic visit date. Patients also received 1-page patient-specific Jumpstart-Tips forms, which summarized their survey responses and provided suggestions for having a goals-of-care conversation with the clinician. Patients in the control group completed the same surveys, but no information was provided to the patients or clinicians. Clinicians were randomly assigned in a 1:1 ratio to intervention or enhanced usual care.

**Main outcome measures.** The primary outcome was patient-reported occurrence of goals-of-care communication, which was evaluated using a validated dichotomous survey item. Other outcomes included clinician documentation of a goals-of-care conversation in the medical record, patient-reported quality of communication (measured using Quality of Communication questionnaire) at 2 weeks, patient reports of goal-concordant care at 3 months, and patient-reported symptoms of depression and anxiety at 3 and 6 months. All analyses included covariate adjustment for the baseline measure of the outcome and adjustment for other variables found to confound the association between randomization group and outcome.

**Main results.** Of 485 potentially eligible clinicians, 65 clinicians were randomized to the intervention group and 69 were randomized to the control group. Of these 132 clinicians, 124 had patients participating in the study: 537 out of 917 eligible patients enrolled, with 249 allocated to intervention and 288 to usual care.

Patients in the intervention group were more likely to

report a goals-of-care conversation with their provider among all patients (74%,  $n = 137$  vs 31%,  $n = 66$ ;  $P < 0.001$ ). Patients who received the intervention also were more likely to report a goals-of-care conversation than those who did not explicitly decline to avoid such discussion (78%,  $n = 112$  vs 28%,  $n = 44$ ;  $P < 0.001$ ). Participating clinician documentation of goals-of-care discussion was also higher for patients in the intervention group among all patients (62%,  $n = 140$  vs 17%,  $n = 45$ ;  $P < 0.001$ ). Compared to clinicians who saw patients that did not explicitly decline the discussion, medical record documentation of goals-of-care discussion was higher for the intervention patients (63%,  $n = 114$  vs 17%,  $n = 34$ ;  $P < 0.001$ ).

Patients in the intervention group also reported higher quality ratings of goals-of-care conversations at the target visit (mean values, 4.6 v 2.1,  $P = 0.01$ , on the 4-indicator construct). Additionally, intervention members reported statistically significant higher ratings on 3 of the 7 individual quality-of-communication survey items.

Patient-assessed goal concordant care did not increase significantly overall (70% vs 57%;  $P = 0.08$ ) but did increase for patients with stable goals between 3-month follow-up and last prior assessment (73% vs 57%;  $P = 0.03$ ). Symptoms of depression or anxiety were not different between groups at 3 or 6 months.

**Conclusion.** The Jumpstart-Tips intervention was associated with an increase in patient reports and clinician documentation of goals-of-care communication. Increased patient-reported goal-concordant care among patients with stable goals was also associated with the intervention. Statistical significance was not detected for changes in depression or anxiety as a result of the intervention. The impact on goals-of-care discussion between patients and caregivers is suggestive of enhanced patient-centered care; however, further studies are needed to evaluate whether this communication is associated with changes in health care delivery.

### Commentary

Previous research has shown that patients with serious illness who discuss their goals-of-care fare better in terms of quality of life and reducing intensity of care at the end-



of-life [1]. However, providers often fail to or inadequately discuss goals of care with seriously ill patients [2,3]. This contributes to the lack of concordance between patient wishes, particularly related to end-of-life care, and clinical plans of care [4,5]. Addressing this gap between care provided and care desired, as well as providing high-quality, patient-centered care is needed.

Access to palliative care providers (who are trained to address these priorities) in the outpatient setting lags, despite an increase in specialists [6,7]. Thus, primary and specialty care providers in the outpatient setting are best positioned to align their care strategy with the goals of their patients. However, there have been limited results in showing that goals-of-care communication can be improved within the practice setting [8,9]. A randomized clinical trial among hospitalized seniors at the end-of-life showed an association where those who received advanced care planning with had improved quality of life, reduced care at dying, and reduced psychological distress among family [10]. However, in another randomized trial, simulation-based communication training compared with usual education among internal medicine and nurse practitioner trainees did not improve quality of communication about end-of-life care or quality of end-of-life care but was associated with a small increase in patients' depressive symptoms [11]. A recent 2018 literature review of strategies used to facilitate the discussion of advance care planning with older adults in primary care settings identified effective interventions, including delivering education using various delivery methods, computer-generated triggers for primary care physicians (PCPs), inclusion of multidisciplinary professionals for content delivery, and patient preparation for PCP visit [12].

This article adds to the literature by demonstrating the feasibility and impact of implementing an intervention to increase communication about goals of care and end-of-life care. Further, this study highlights how communication that is bilateral, predetermined, and structured can be integrated into primary care. Strengths of the study include the use of randomization; deployment of validated survey tools; and confirmatory factor analysis to assess whether the survey variables are consistent with the hypothesized constructs. In addition, study staff were blinded when extracting data from the

EHR record around discussions and documentation of goals-of-care conversations during patient visits. However, several limitations are present. There may be limited generalizability as the study was performed at low-scale, across one region as well as selection bias among clinicians participating in the study. Clinicians were not blinded of their assignment, which may have influenced their behaviors to discuss and document goals-of-care conversations.

### Applications for Clinical Practice

Increasing quality communication around the end of life and understanding of a patient's goals is important. Good communication can facilitate the development of a comprehensive treatment plan that is medically sound and concordant with the patient's wishes and values. Clinicians and practices should consider adopting approaches to communication priming and accurate documentation, including: (1) incorporating/automating Jumpstart-Tips forms into practice (and tailoring as needed); (2) identifying similar education material that can serve as a primer for patients; (3) creating a pre-visit form for patients/caregivers to document and inform the clinician of their goals prior to the visit; (4) incorporating a standard EHR note to document and update goals-of-care discussion at each visit; and (5) more broadly encouraging (or providing training for) clinicians to practice bilateral communications with patients during visits.

—Ronald Sanchez, MPH, and Katrina F. Mateo, MPH

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