

Treatment Extension to 72 Weeks of Peginterferon and Ribavirin in Hepatitis C Genotype 1–Infected Slow Responders

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In hepatitis C virus (HCV) genotype 1 infection, the duration of interferon-based therapy is a critical determinant in achieving sustained virologic response (SVR). Slow or late responders to peginterferon and ribavirin may benefit from an extended treatment course. We sought to determine if therapy extension could improve response rates in a United States population of slow responders. Slow response was defined by achieving at least a 2-log decrement in HCV RNA from baseline, yet having detectable HCV RNA at 12 weeks and undetectable HCV RNA at 24 weeks (polymerase chain reaction, TaqMan, Roche; detection limit 10 IU/mL). Patients were treatment-naïve, chronically infected genotype 1–infected slow responders to 1.5 µg/kg/week of peginterferon-α2b and 800–1400 mg/day of ribavirin and were randomly assigned 1:1 to complete a total of 48 or 72 weeks of therapy. Dose reductions and treatment discontinuations for adverse events or laboratory abnormalities were similar between the 2 treatment arms. End-of-treatment response rates were similar in the 72-week group compared with those in the 48-week group (48% versus 45%; *P* value not significant). Overall, the rate of SVR was superior in patients treated for 72 weeks versus 48 weeks (38% versus 18%, respectively; *P* = 0.026). **Conclusion:** Extending the treatment duration from 48 weeks to 72 weeks in genotype 1–infected patients with slow virologic response to peginterferon-α2b and weight-based ribavirin significantly improves SVR rates. Treatment extension does not seem to increase the rate of dose reduction or therapy discontinuation. (HEPATOLOGY 2007;46:1688–1694.)

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The current standard of care for the treatment of chronic hepatitis C is peginterferon and ribavirin, which can induce a sustained virologic response (SVR) in the majority of patients treated.^{1,2} However, patients infected with hepatitis C virus (HCV) genotype 1 achieve SVR less frequently, especially those who have high viral loads and who are African American.^{1–4}

Although treatment for genotype 1–infected patients is typically given for 48 weeks, there has been interest in extending therapy duration, particularly in slow-responders.⁵ Patients treated with peginterferon and ribavirin who do not achieve a 12-week early virologic response (defined by an undetectable serum HCV RNA level or >2-log decrease relative to a pretreatment RNA level) have only a 3% or lower chance of achieving an SVR.^{6,7} However, there is an important dichotomy in response rate between patients who, after 12 weeks of therapy, attain undetectable serum viral RNA versus patients who achieve at least a 2-log decrement in baseline HCV RNA yet still have detectable viremia. In a retrospective analysis of the registration trial for peginterferon-α2b plus ribavirin, patients in the latter group achieved SVR about one-fourth as frequently as patients in the former group.⁷ The latter patients are said to be slow or late responders to therapy. Slow responders have also been characterized as those with detectable viremia at 4 weeks of therapy; either definition necessitates undetectable virus in the serum after 24 weeks of therapy. High relapse rates in patients with slow virologic response may indicate that treatment was

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

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not administered for a sufficient duration.⁶ Thus, prolonging therapy in patients who are slow responders to treatment may improve virologic response rates.

Two prospective studies from Europe have demonstrated that slow responders had improved SVR rates when treated for 72 weeks, compared with standard duration of therapy, largely as a result of reducing posttreatment relapse rates.^{8,9} However, these trials used suboptimal doses of ribavirin for genotype 1 infection (800 mg/day). Furthermore, it is unclear if treatment extension could benefit more treatment-resistant patients such as African Americans and those with advanced fibrosis on liver biopsy.

We sought to determine if treatment extension could improve response rates in a United States population of slow responders using weight-based ribavirin dosing.

Patients and Methods

Patients. Chronic HCV genotype 1–infected patients were eligible for enrollment if they fulfilled the following pretreatment criteria: baseline elevated serum alanine aminotransferase levels, detectable serum HCV RNA via nucleic acid testing, HCV genotype 1, treatment-naïve, age ≥ 18 years, and a liver biopsy in the past 2 years consistent with chronic hepatitis. Before randomization, patients had been slow responders to 24 weeks of subcutaneous peginterferon- $\alpha 2b$ (1.5 $\mu\text{g}/\text{kg}/\text{week}$) (Peg-Intron; Schering-Plough, Kenilworth, NJ) and oral ribavirin (800–1400 mg/day based on weight: ≤ 64 kg, 800 mg; 65–84 kg, 1000 mg; 85–104 kg, 1200 mg; ≥ 105 kg, 1400 mg). A slow responder was defined as a patient with at least a 2-log decrement in baseline serum HCV RNA, albeit detectable viremia at 12 weeks and undetectable serum HCV RNA at 24 weeks with the same assay (polymerase chain reaction, Taqman, Roche; detection limit 10 IU/mL). All testing was performed at a single reference laboratory.

Pretreatment exclusion criteria included the following: HCV/human immunodeficiency virus coinfection; HCV genotype other than 1; decompensated cirrhosis; other causes of liver disease, including coinfection with hepatitis B; creatinine clearance < 50 mL/minute (modification of diet in renal disease equation); platelet count $< 80 \times 10^9/\text{L}$; neutrophil count $< 1.5 \times 10^9/\text{L}$; hemoglobin concentration < 13 g/dL and 12 g/dL in men and women, respectively; coexisting uncontrolled psychiatric or cardiopulmonary disorders; hemoglobinopathy; sarcoidosis; malignant neoplasm; receipt of immunosuppressive or immunomodulatory therapy in the previous 6 months; pregnancy; and men whose partners were pregnant or unwilling to use contraception during the study period.

Patients were also excluded if they imbibed significant amounts of alcohol (> 30 g/day), or if they were active substance abusers in the past 6 months.

Patient characteristics recorded at baseline included age, sex, body mass index, fasting glucose, ethnicity, histological results of pretreatment liver biopsy (Metavir scoring: F0, no fibrosis; F1, portal fibrosis; F2, few septa; F3, many septa without cirrhosis; F4, cirrhosis), and quantitative HCV viral load (recorded as IU/mL at baseline and at 12 and 24 weeks of therapy).

The study was investigator-initiated. The protocol was approved by Atlanta Medical Center's Institutional Review Board, and all patients gave written informed consent to participate. The trial adhered to the ethical principles outlined in the World Medical Association Declaration of Helsinki. Patients were recruited from Atlanta Medical Center's Center for Hepatitis C and Sheffield Health Center, both ambulatory clinics, in downtown Atlanta, Georgia. Schering-Plough, the manufacturer of peginterferon- $\alpha 2b$, had no direct or indirect involvement in the study design, data collection, or preparation of the manuscript.

Treatment and Monitoring. Slow responders were randomly assigned in a 1:1 ratio to continue therapy for an additional 24 weeks (customary total treatment duration of 48 weeks; group A) or to extended therapy for an additional 48 weeks (total treatment duration of 72 weeks; group B). Therapy dosing was not changed between prerandomization and postrandomization; patients received subcutaneous 1.5 $\mu\text{g}/\text{kg}/\text{week}$ of peginterferon- $\alpha 2b$ and 800–1400 mg/day of ribavirin, unless the dose had been reduced for cytopenias during the initial 24 weeks of treatment. Growth factors were specifically prohibited.

Patients were monitored at baseline and at monthly intervals via physical examination, patient weight, Beck's Depression Inventory, complete blood count and differential, hepatic profile, thyroid-stimulating hormone, electrolytes, serum creatinine, serum uric acid, and serum beta-human chorionic gonadotropin levels, if applicable. Standard dose reduction protocols were followed; 200 mg ribavirin dose reductions and 0.5 $\mu\text{g}/\text{kg}$ peginterferon dose reductions were used. However, for interferon-related neutropenia, dose reductions and treatment discontinuations were made only for absolute neutrophil counts under $0.5 \times 10^9/\text{L}$ and $0.25 \times 10^9/\text{L}$, respectively. An end-of-treatment response was checked via serum RNA analysis (polymerase chain reaction, Taqman, Roche; detection limit 10 IU/mL) at week 48 (group A) and at week 72 (group B), and again to assess SVR 24 weeks after therapy cessation. SVR was the primary endpoint; relapse rate was the secondary endpoint.

Statistical Analysis. The analysis was conducted on an intent-to-treat basis—though, in fact, all patients received at least an initial dose of postrandomization therapy. Physicians enrolled participants and obtained informed consent to participate. Only randomized patients were included in outcome analyses. Patients were randomized to 1 of 2 study treatment durations at a ratio of 1:1 without stratification, and randomization groups were concealed until after patients consented to participate and interventions were assigned. Data were collected by a research nurse not involved in the patients' treatment (independent, contracted research company). Patient baseline characteristics were compared using chi-square tests, and all outcome and subgroup analyses were performed using the same chi-square tests and applying the Yates correction factor when indicated by sample size. A P value of <0.05 was considered significant. Because population power estimates and expected frequencies were not specified beforehand, only nonparametric statistics were possible. The study was designed to randomize 100 slow responders to 1 of 2 alternative treatment durations; thus, after 100 patients were assigned to treatment, enrollment ceased. Except for an abstract submission in April 2006, at which time data were analyzed from patients who had finished treatment to date, outcome data were reviewed only after the entire group of randomized patients had completed therapy. We chose to enroll 100 patients, believing that this number would be an adequate and representative sample of slow responders to therapy; the number was not generated from a formal sample size calculation.

Results

Patient Profiles. Patients were recruited between June 2003 and September 2005 from 2 separate ambulatory clinics at our single center. The trial participant flow is shown in Fig. 1. Of 361 patients with genotype 1 infection treated with peginterferon and ribavirin during that study period, 112 patients (31%) were slow responders to therapy and met inclusion criteria. However, only 101 patients participated and were randomized. Eleven slow responders either declined to participate in the study or were ineligible.

One hundred one slow responders were assigned to group A ($n = 49$) or group B ($n = 52$). Groups A and B had statistically similar characteristics with respect to baseline demographic, biochemical, and virologic features as shown in Table 1. The mean age was 56 years in the standard duration group and 54 in the extended duration group (age ranges in years were 25-66 and 30-65, respectively). At week 12 of therapy, there was no significant

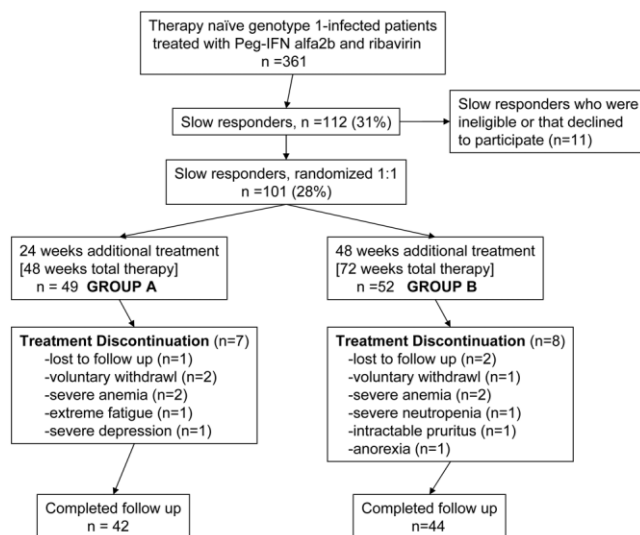


Fig. 1. Study participant flow.

difference in mean HCV RNA serum concentrations between group A and B.

Side Effects. Neither dose reductions nor therapy discontinuations were statistically different between treatment arms (Fig. 2). Between treatment weeks 1 through 24 (prerandomization), 29 patients' medication was dose-reduced (in 14 and 15 patients from groups A and B, respectively). However, only 1 of these patient's peginterferon doses was reduced; the remainder had a single ribavirin dose reduction in a 200-mg decrement relative to starting dose (thus receiving 600-1200 mg ribavirin daily). All of these dose reductions took place in the first 19 weeks of therapy.

Fewer dose reductions were needed between weeks 24 and 48 in treatment arms A and B (4 and 2 patients, respectively). Only 1 patient in group A required concomitant peginterferon and ribavirin dose reduction during this treatment interval. Only 1 ribavirin dose reduction was necessary between weeks 48 and 72 (extended duration arm).

Regarding treatment cessation, 14% of patients ($n = 7$) in the standard duration arm and 15% of patients ($n = 8$) in the extended therapy arm discontinued treatment (Fig. 1). All therapy cessation occurred between weeks 24 and 48 of treatment in both arms; none of the therapy discontinuations in the extended duration arm occurred between weeks 48 and 72.

Viral Response. Although there was no statistical difference between groups A and B in the end-of-treatment response [22/49 (45%) patients versus 25/52 (48%) patients, respectively], SVR, the primary endpoint, was statistically superior in the extended treatment arm [20/52 (38%) patients versus 9/49 (18%) patients in the stan-

Table 1. Summary of Patient Baseline Characteristics

Pretreatment Characteristic	All Patients with Slow Response to Therapy (n = 101)	Slow Responders Treated for 48 Weeks (n = 49)	Slow Responders Treated for 72 Weeks (n = 52)	P Values for 48 Versus 72-Week Treatment Groups
Patients with F3/F4 Fibrosis (%)	26 (n = 26)	27 (n = 13)	25 (n = 13)	0.86
Patients with high viral load* (%)	78 (n = 79)	80 (n = 39)	77 (n = 40)	0.75
Body mass index (kg/m ²) ≥30 (%)	34 (n = 34)	33 (n = 16)	35 (n = 18)	0.84
Fasting glucose (% over 100 mg/dL)	18 (n = 18)	18 (n = 9)	17 (n = 9)	0.89
African American subjects (%)	48 (n = 48)	47 (n = 23)	48 (n = 25)	0.91
Male subjects (%)	66 (n = 67)	67 (n = 33)	65 (n = 34)	0.84
Mean baseline viral load (×10 ⁶ IU/mL)	5.3	5.3	5.4	NA
Mean 12-week viral load (IU/mL)	17,944	17,637	18,384	NA
Mean body mass index (kg/m ²)	28.9	28.8	29.1	NA
Mean age (years)	55	56	54	NA

Abbreviations: F3/F4 fibrosis, bridging fibrosis/cirrhosis on METAVIR staging. *HCV viral load greater than or equal to 800,000 IU/mL; NA, not applicable.

dard duration arm] (Fig. 3). A lower relapse rate was noted in group B [5/25 (20%) patients versus 13/22 (59%) patients in group A]. No statistically significant difference was noted between groups A and B in subgroup analysis (data not shown). However, African American slow responders did show significant improvement in SVR rates when treatment was extended (end-of-treatment response rate, 24% versus 26%, *P* value not significant; SVR rate, 12% versus 21%, *P* = 0.02 in groups A and B, respectively).

In the intention-to-treat analysis of the 249 genotype 1–infected, treatment-naïve patients not classified as slow responders, the end-of-treatment response rate was 51% with an SVR rate of 36%.

Discussion

A 48-week regimen of peginterferon has become the standard of care for chronic HCV patients with genotype 1 infection.¹⁰ However, these patients’ SVR rates remain suboptimal, especially in those with unfavorable pretreatment characteristics.¹⁻³ We attempted to improve re-

sponse rates in a population of genotype 1–infected slow responders by extending treatment duration to 72 weeks.

Some investigators have hypothesized that the longer the duration of serum HCV RNA undetectability during treatment, the better the probability of an SVR. Analyzing data from a phase III randomized trial of pegylated-α2a and ribavirin, Drusano and Preston¹¹ developed a prediction model based on the duration of viremia suppression. Because the average time to clear serum entirely of HCV genotype 1 was over 30 weeks, the authors concluded that the standard, 48-week duration of therapy was inadequate for most patients with this genotype. In another analysis from a large treatment trial, Ferenci et al.⁶ concluded that patients on treatment with the slowest diminution rates of viremia had relatively poor response rates compared with those of more rapid responders. In fact, slow responders to therapy had high relapse rates. Thus, therapy prolongation in “late” responders to interferon could potentially improve rates of SVR.

Treatment extension is not a new concept in HCV therapy. Using standard interferon, several authors have

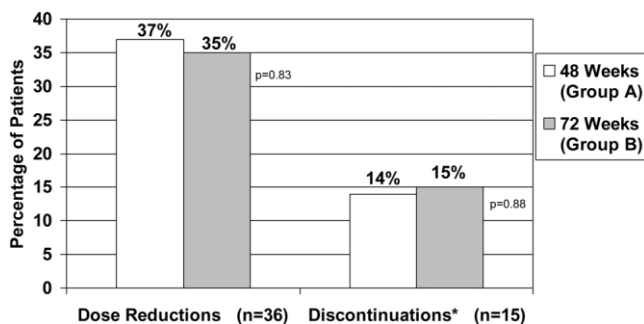


Fig. 2. Dose reductions and treatment discontinuations. No statistically significant differences were seen between slow responders treated for 48 weeks versus those treated for 72 weeks. *Includes both adverse events and therapy discontinuations.

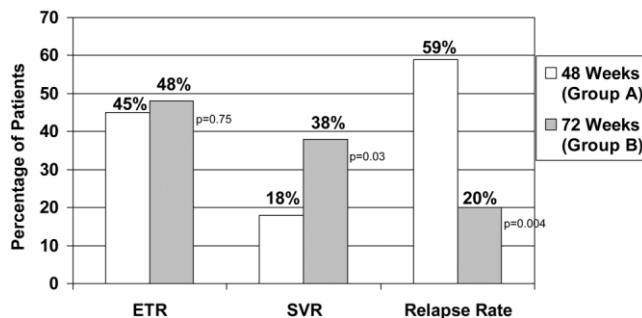


Fig. 3. Overall response rates in slow responders treated for 48 weeks versus 72 weeks. Patients treated for 72 weeks had significantly improved rates of sustained response compared with those treated for 48 weeks, largely because of a diminution of posttreatment relapses. ETR, end-of-treatment response rate; SVR, sustained virologic response rate.

demonstrated improved biochemical, histological, and virologic responses with treatment ranging from 60 to 76 weeks compared with treatments of shorter durations.^{12,13} In a randomized, controlled trial, extension of treatment from 6 to 18 months with standard interferon and ribavirin had an independent effect on relapse and SVR rates in genotype 1 infection.¹⁴ Treatment prolongation may likewise be beneficial with newer therapies. Seventy-two weeks of peginterferon- α 2b (1.0 μ g/kg/week) and ribavirin (800 mg/day) achieved impressive response rates (when compared with those of a historical control) in a small group of slow responders to therapy.⁵ In a subgroup analysis from a German multicenter trial,⁸ slow responders to peginterferon- α 2a (180 μ g/week) and ribavirin (800 mg/day) showed statistically superior rates of SVR when treated for 72 weeks compared with 48 weeks. Similarly, in a multicenter trial from Spain using peginterferon- α 2a (180 μ g/week) and ribavirin (800 mg/day), slow responders benefited from 72 weeks of treatment relative to 48 weeks.⁹ In both studies, treatment extension improved slow responders' response rates, largely as a result of diminished rates of relapse.

However, both of the aforementioned studies used suboptimal doses of ribavirin; weight-based ribavirin dosing is necessary for improved SVR rates in HCV genotype 1 infection.¹⁵ In the Spanish study,⁹ patients were not exclusively genotype 1–infected. Furthermore, because response rates correlate negatively with body weight,¹⁶ it is unclear if either study applies to United States patients whose body mass indexes are typically greater than their European counterparts. Applicability to United States populations is also uncertain because African Americans, a group with inferior response rates relative to those of Caucasians, were not studied.^{3,4,17} Finally, in the German trial,⁸ over 90% of patients studied had stage 2 or milder fibrosis (METAVIR). Thus, it is unclear if treatment extension could benefit slow responders with bridging fibrosis or compensated cirrhosis or with other pretreatment characteristics that adversely impact SVR rates, particularly when using weight-based doses of ribavirin.

One hundred twelve (31%) of our treatment-naïve patients were deemed slow responders to combination therapy, which included weight-based ribavirin; those studied ($n = 101$) had baseline characteristics that made them difficult to treat. Our percentage of slow responders is higher than that observed in the study of Berg et al.⁸ (slow responders were between 20% and 23% of all patients treated), likely because of unfavorable pretreatment characteristics. All of our patients were genotype 1–infected. More than three-fourths of patients in either treatment arm had high viral loads, and 24% of those studied had advanced fibrosis or worse on liver biopsy. Moreover, at

least one-third were obese, and nearly one-half identified themselves as African American.

In an intention-to-treat analysis of our slow responders randomized to 48 versus 72 weeks of therapy, SVR rates were statistically superior in the extended treatment arm. Because the end-of-treatment response rates were similar in both groups (P value not significant), treatment extension seemed to benefit slow responders by virtue of a decrement in relapse rate. This pattern mirrored that of the aforementioned trials from Spain and Germany, reinforcing the hypothesis that a longer suppression of viremia is necessary to ultimately achieve SVR in those patients who respond to therapy late.

Our study was similar to the European trials in that neither the number of dose reductions nor the number of adverse events was statistically different between treatment arms. However, unlike the other studies, we did not see a greater discontinuation rate in our extended treatment duration arm compared with that in the standard treatment duration arm. In fact, none of the treatment discontinuations in the extended arm occurred between 48 and 72 weeks. In other words, no patient experienced “therapy fatigue” because the extended treatment duration was too arduous. It is unclear why our patients' adherence rates were relatively superior to those in the European studies. We surmise that improved adherence was the result of physician-driven care and continuity, because 90% or more of our patients were seen by the same treating physician on a monthly basis throughout the trial. Furthermore, a low attrition rate in the extended treatment arm could be explained by the patients' knowledge before treatment that up to 72 weeks of therapy might be required for maximal benefit.

Because of prerandomization dose reductions between weeks 1 and 24 of treatment, 28 of our 101 slow responders were treated with suboptimal doses of ribavirin for the remainder of their therapy courses. Nonetheless, all were single-step ribavirin dose reductions of 200 mg, relative to the therapy initiation dose. We do not believe that this had any impact on the results. Apparently, only a reduction in cumulative ribavirin dose to less than 60% of the original intended dose has an adverse effect on SVR rates.¹⁸ Furthermore, as long as patients receive full-dose peginterferon—as did all slow responders who completed therapy in our study, with one exception—ribavirin dose reduction in the first 20 weeks of treatment has virtually no effect on SVR rates.¹⁹

Dose reductions for therapy-related neutropenia were infrequent, because we lowered the threshold for peginterferon dose reductions and discontinuations relative to medication package labeling guidelines. As was seen in prior studies,^{17,20,21} low absolute neutrophil counts were

not associated with episodes of febrile neutropenia or life-threatening infections.

Nearly 50% of our randomized patients were African American, a group with inferior virologic response rates relative to those of Caucasians.²² Nonetheless, African American slow responders enjoyed improved response rates with treatment extension to 72 weeks compared with rates using a standard therapy duration. This information might be useful in our search to find more effective therapies for the African American population. However, because response rates were derived from a subgroup analysis, these results should be interpreted with caution.

The primary limitation of our study was that it was conducted in a single medical center without a priori power determinations and expected outcome parameters. Thus, we cannot exclude a type II error. However, generalizability and ability to extrapolate to similar populations was augmented, because patients were treated in 2 independent ambulatory clinics, and the results mirrored those of Berg et al.⁸ and Sanchez et al.⁹ Furthermore, as in the aforementioned trials, our study was not blinded in that placebo was not administered from weeks 48 to 72 in the control arm; such treatment would have necessitated sham injections. Another study limitation was that biochemical or histological improvements were not assessed; 72 weeks of therapy could have improved liver histology irrespective of the absence of virologic response. In addition, with the exception of African Americans, our subgroup analysis was extremely limited, because there were too few patient numbers in each subgroup to make statistically or clinically meaningful conclusions. For example, we could not confidently conclude that treatment extension benefited those with a baseline high viral load and not those with low levels of viremia pretreatment. Another study shortcoming was that very few patients had a serum HCV RNA checked at 4 weeks after therapy was initiated; the practice had not been popularized at the time of our protocol formulation. Finally, we did not assess any treatment-experienced patients in our study. It is unclear if relapsers or nonresponders to prior therapy could benefit from treatment prolongation beyond 48 weeks.

In conclusion, extending the treatment duration from 48 to 72 weeks in chronically infected HCV genotype 1 patients who have unfavorable pretreatment characteristics and slow response to peginterferon- α 2b and weight-based ribavirin significantly improves SVR rates. Treatment extension does not seem to increase the rate of dose reduction or treatment discontinuation. Results

should be confirmed in multicenter trials; we await the final results of the SUCCESS trial,²³ a multicenter study of slow responders using a similar treatment extension strategy.

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