

By March, the efforts of the associate editors and the 34-member-strong Board of Reviewing Editors to spur submissions began to bear fruit, and by July 1990 we had enough manuscripts to fill three issues of *JASN*. We had a welcome reprieve in October because only meeting abstracts were published in that issue. We would survive!

The next hurdle we faced was getting *JASN* indexed in the Library of Medicine's Medline/Index Medicus, the antecedent of PubMed. Journals not included in the citation index were dead in the water. The editors, ASN Council, and mystery supporters worked hard to win approval, and after 2 yr, *JASN* was admitted and retrofitted to the July 1990 issue. It was shocking to us all when the first *Impact Factor* for *JASN* was two points higher than our close rival, *Kidney International*, whose editor, Thomas E. Andreoli, was on the ASN Council and scheduled to become president. Tom was certain that the Institute for Scientific Information (ISI; now Thomson/Reuters) had counted ASN Meeting abstract citations in the numerator of the *Impact Factor* because it was common practice back then to cite these in publications. Williams and Wilkins, *JASN*'s publisher at the time, investigated and found no evidence of such mischief. It is interesting to note that *JASN* has maintained its top rating among all kidney and urology titles long after the abstracts stopped being published in a regular issue.

In preparation for the 20th anniversary celebration, Lawrence Sullivan and I reexamined the July 1990 issues of *JASN* and *Kidney International* and determined the total citations in Google Scholar for the 10 articles published in *JASN* and the first 10 articles published in the comparable issue of *Kidney International*. Twenty years later, *JASN* still wins 342 to 264. To their credit, Tom Andreoli and Saulo Khlar, Tom's successor at *Kidney International*, always treated *JASN*'s editors as good friends and trusted colleagues. We believe that this collegial spirit and mutual respect within our international academic discipline have contributed to both journals' growing ever stronger through the years.

We invite readers to peruse the inaugural 1990 issue of *JASN*, including our editorials. There we forecast, correctly we are pleased to report, the continued exciting growth of a field of inquiry that was the first to bring the basic and clinical sciences into a mutually supportive relationship. Over the past 20 yr, the field of nephrology has truly excelled with a notable exception. The National Kidney and Urology Advisory Board (NKUDAB), composed of 21 physicians, surgeons, scientists, and lay leaders from across the United States, together with key government administrators, published an executive summary outlining recommendations developed over 3 yr of study and deliberation. The NKUDAB recommended in the inaugural 1990 issue that Congress establish a new National Institute of Kidney and Urologic Diseases within the National Institutes of Health (NIH), Congress appropriate an additional \$300,000 to the NIH for the Division of Research Grants to establish a nephrology study section, and Congress appropriate an additional \$300,000 to the NIH for the Division of Research Grants to establish a urology study section. Sadly, these goals were never realized, because momentum for them waned with successive changes in ASN leadership.

In one of the editorials in that inaugural issue, we stated that we wanted *JASN* to do more than merely archive data; rather, we ex-

pected it to facilitate an interaction among nephrologists, molecular biologists, physiologists, biochemists, immunologists, and pathologists that was occurring and still does occur at the annual ASN meeting. In other words, we wanted *JASN* to promote a dialogue among investigators, practitioners, and students who recognize what Homer Smith so eloquently proclaimed: "The kidney makes the stuff of philosophy itself." Looking back on the first 20 yr of *JASN*, we think that we met that goal.

In August 1996, we turned the reins of *JASN* over to Craig Tisher at his cabin in the Black Hills of South Dakota.

Bonnie O'Brien, seeing an opportunity to live in tennis heaven, accepted the new editor's offer of continued employment in Florida. She is now working with her fourth editor. *JASN* has changed its physical appearance and secondary internal features with each new editor, yet the scientific content and the publication timelines just keep getting better and Bonnie O'Brien just keeps rollin' along.

Shortly before we closed the door to the *JASN* office at the University of Kansas for the last time, the departing editors and Bonnie O'Brien opened a bottle of Shiraz and recalled the words of the Danish novelist Isak Dinesen: "What is man, when you come to think upon him, but a minutely set, ingenious machine for turning, with infinite artfulness, the red wine of Shiraz into urine?"

Does TREAT Give the Boot to ESAs in the Treatment of CKD Anemia?

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"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way."

Charles Dickens, *A Tale of Two Cities*, 1859¹

The recently published landmark study the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT)² has turned the world of anemia management upside down. Patients who have chronic kidney disease (CKD) and anemia and literally could not get up in the morning will despair that insurance com-

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panies will put erythrocyte-stimulating agents (ESAs) beyond their reach. Insurance companies and Medicare may look at this as the “season of Light.” TREAT provides definitive evidence to justify making tough reimbursement decisions: Restricting the use of ESAs to symptomatic patients or those who are awaiting kidney transplantation.

Some in the academy will view the era before the anemia trials as “the age of foolishness”: ESA treatment decisions and guidelines based on flawed data using hemoglobin (Hb) as a nonvalidated surrogate. Biotechnology companies looking to bring a new epoetin molecule to the market might view this as “the season of Darkness” because the market for their new drug has just vaporized; however, my guess is that most nephrologists will be confused, some perhaps incredulous. How should the results of the TREAT study and those of the major anemia trials preceding it be interpreted in terms of making decisions about treating individual patients?

TREAT² is a placebo-controlled, double-blind, randomized study that comprised 4038 patients and was neutral for its primary composite end points: Death or a cardiovascular event occurred in 632 patients assigned to darbepoetin- α and 602 patients assigned to placebo (hazard ratio [HR] for darbepoetin *versus* placebo 1.05; $P = 0.41$). Death or ESRD occurred in 652 patients assigned to darbepoetin and 618 patients assigned to placebo (HR 1.06; $P = 0.29$); however, there was a significantly higher rate of strokes in patients treated with darbepoetin. Fatal or nonfatal strokes occurred in 101 patients assigned to darbepoetin and 53 patients assigned to placebo (HR 1.92; $P < 0.001$). A higher rate of both thromboembolism (and deep venous thrombosis [DVT]) in the darbepoetin-treated patients was also observed. Among 2012 patients in the darbepoetin group, 39 (1.9%) deaths were attributed to cancer compared with 25 (1.2%) deaths among the 2026 patients on placebo ($P = 0.08$). Among patients with a history of malignancy at baseline, there were 60 deaths from any cause in 188 (31.9%) patients assigned to darbepoetin and 37 (23.1%) deaths in 160 placebo patients ($P = 0.13$). In this subgroup, 14 (7.4%) of the 188 patients assigned to darbepoetin died from cancer compared with one (0.62%) of the 160 patients assigned to placebo ($P = 0.002$). There also was a significantly higher risk for red cell transfusions among patients assigned to placebo. Conversely, there was only a modest improvement in patient-reported quality of life between the darbepoetin and placebo arms.

Three large studies, including TREAT, of nondialysis patients with CKD have tested the hypothesis that normalization of Hb with ESA associates with improvement in cardiovascular, renal, and mortality outcomes; the other two are Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin- β (CREATE). CHOIR³ was an open-label, randomized trial that studied 1432 patients who had CKD and were receiving epoetin- α targeted to achieve a Hb of 11.3 g/dl. The median study duration was 16 mo. The primary end point was a composite of death, myocardial infarction, congestive heart failure, hospitalization, and stroke. A total of 125 events occurred among the high-Hb group and 97 events among the low-Hb

group (HR 1.34; $P = 0.03$). The higher rate of composite events was explained largely by a higher rate of death (48% higher risk; $P = 0.07$) or congestive heart failure hospitalization (41%; $P = 0.07$). Among other secondary end points, quality of life improved in both groups but was not significantly better in the high- *versus* low-Hb group.

CREATE⁴ enrolled approximately 600 patients. Patients were randomly assigned to an early or a late anemia correction group. The early group received epoetin- β therapy immediately for a target Hb 13 to 15 g/dl. The late anemia correction group did not receive treatment until their Hb was < 10.5 g/dl; their target Hb was 10.5 to 11.5 g/dl. Complete correction was not associated with a higher rate of the first cardiovascular event (HR 0.78; $P = 0.20$); however, left ventricular mass remained stable in both groups, but dialysis was required in more patients in the higher compared with lower Hb groups (127 *versus* 111; $P = 0.03$). Unlike CHOIR, quality of life measured using the SF-36 showed statistically significant improvement in several domains in patients assigned to the higher (and early anemia treatment) Hb arm.

How does one reconcile the results of these three studies? In each, there was either no benefit or increased risk for mortality or cardiovascular complications. In CREATE, the point estimate of risk in the direction of harm was 22% (95% confidence interval [CI] 0.53 to 1.14), in CHOIR 34% (95% CI 1.03 to 1.74), and in TREAT 5% (95% CI 0.94 to 1.17), respectively. In other words, targeting a higher Hb concentration with ESAs was certainly not associated with benefit but perhaps increased risk. Moreover, in TREAT comparing an ESA with placebo, there was no benefit in terms of hard outcomes. In CHOIR and TREAT, there were disparate adverse signals: In CHOIR, death and heart failure were observed in patients targeted to a higher Hb (13.5 g/dl), whereas, in TREAT, a higher risk for stroke was observed in darbepoetin-treated patients.

Could this heterogeneity reflect the use of different ESAs? In other words, is this a class effect? In CHOIR, epoetin- α was tested; in TREAT, the study drug was darbepoetin- α ; and in CREATE, epoetin- β was used to target higher Hb levels. There are well-documented biologic differences between epoetin- α and darbepoetin- α and, in turn, between epoetin- α and its derivative darbepoetin- α and epoetin- β .^{5–7} Darbepoetin- α differs from epoetin- α : Darbepoetin contains five N-linked oligosaccharide chains and up to 22 sialic acids, a molecular weight of 37,100 Da, and a carbohydrate composition of 51%. In contrast, epoetin- α has three N-linked carbohydrate chains, a maximum of 14 sialic acids, a molecular weight of 30,400 Da, and a 40% carbohydrate composition.^{5–7} The additional carbohydrates are accommodated by substitutions at five positions along the 165–amino acid backbone. The result is a longer half-life, increased biologic activity, and decreased receptor affinity for darbepoetin compared with epoetin- α .⁵ Indeed, the electropherogram of epoetin and darbepoetin demonstrate quite distinct isoform patterns.⁷ Similarly, Storrington *et al.*⁸ published evidence of biologic differences between epoetin- α and epoetin- β —different isoform patterns, receptor binding charac-

teristics, and murine *in vitro* and *in vivo activity*—therefore, it is possible that a class effect might influence the heterogeneity of clinical outcomes reported in the three major anemia trials.

Could the heterogeneity of the adverse clinical outcomes reflect the enrollment of different populations? In TREAT, all enrolled patients had diabetes; in CHOIR, approximately half of the patients had diabetes; but in CREATE, only approximately 25% of the patients had a history of diabetes. In a recent article evaluating CHOIR subgroups,⁹ we presented evidence that comorbidities may result in differential clinical signals. Observational studies also support diabetes as a comorbid factor that increases mortality risk among patients with CKD and anemia.¹⁰

Another possibility is that exposure to higher and different dosages of ESAs in the three trials could explain the observed risk. In CHOIR, the higher Hb arm received a median of 10,952 U/wk; in TREAT, the median dosage was 8800 U/wk in the darbepoetin arm; and in CREATE, a median dosage of 5000 U/wk epoetin-beta was used in the higher Hb arm. Toxicity from high ESA dosage is suggested by several studies^{11–13} and debated.¹⁴ Hence, it is possible that escalation in epoetin dosage might explain some of the heterogeneity in the severity of the adverse clinical signals.

CHOIR, CREATE, and TREAT differ in blood transfusion rates, perhaps not surprising. In CHOIR, 115 (8.1%) of 1422 patients required a blood transfusion within 6 mo of randomization (unpublished data): 60 (8.5%) of 707 in the higher (13.5 g/dl) Hb arm and 55 (7.7%) of 715 in the lower (11.3 g/dl) Hb arm. In CREATE, overall, 59 (9.8%) of 603 patients required blood transfusion: 26 (8.6%) of 301 patients in the higher Hb group and 33 (10.9%) of 302 patients in the lower group. In contrast, nearly twice as many patients assigned to placebo *versus* darbepoetin (496 patients (24.5%) required blood transfusions *versus* 297 patients (14.8%; $P < 0.001$), respectively. These data point to a higher risk for red cell transfusions when adopting a strategy based on the placebo arm of TREAT.

The patient-reported outcomes in CHOIR and TREAT seem concordant in that quality-of-life measure improved in both arms of the study, whereas CREATE seems to be an outlier because quality of life deteriorates in the lower Hb arm and improves in patients assigned to the higher Hb. Patient-reported outcomes were assessed in TREAT using the FACT-fatigue and SF-36 instruments; in CHOIR, patient-reported outcomes were evaluated using the Linear Analogue Scale Assessment (LASA), Kidney Disease Questionnaire (KDQ), and SF-36; and in CREATE using only SF-36. In TREAT, using FACT-fatigue, there was an increase in the mean \pm SD fatigue score of 4.2 ± 10.5 points in the darbepoetin group *versus* 2.8 ± 10.3 points in the placebo group ($P < 0.001$ for between-group changes). In CHOIR, LASA demonstrated an increase in both groups: In the higher Hb group, there was an increase in the mean \pm SD score for energy of 16.6 ± 28.6 *versus* 15.5 ± 28.6 in the lower Hb group ($P = 0.67$ for between-group changes). CREATE did not use a specific energy or fatigue instrument; therefore, a comparison is not possible. Conversely,

all three studies used the SF-36 instrument. Although no significant differences for the domains of energy and physical functioning were observed in either CHOIR or TREAT, a significant difference was observed for these domains in CREATE. What explains the SF-36 findings between TREAT and CHOIR on the one hand and CREATE on the other? As Coyne¹⁵ noted elsewhere, patients in CREATE knew to which arm they were randomly assigned, and, during the first year, 98% of patients in the high arm received injections whereas only 32% did in the low arm. As well, the patients in the low arm had to develop worsening anemia before institution of epoetin therapy. The differences in quality of life observed in CREATE abated with time despite continued separation in mean Hb levels between groups.

In summary, the results from CHOIR, CREATE, and TREAT should be viewed as complementary rather than contradictory, demonstrating increased risk at higher Hb concentrations and higher ESA dosage; however, unlike CHOIR and CREATE, which were open-label studies comparing one Hb target with the other, TREAT was double-blind in design and compared darbepoetin against placebo. The importance of TREAT should not be understated. Against placebo, ESAs confer no benefit in mortality or cardiovascular or renal outcomes but do demonstrate a higher risk for stroke, thromboembolism, and possibly cancer. There was a lower rate of transfusions with darbepoetin but with only a modest improvement in fatigue. TREAT lays bare the question, “Is the risk of treating with ESAs patients who have CKD and anemia worth it?”

How should nephrologists manage CKD anemia? With the publication of TREAT, the 2007 revised Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines¹⁶ as well as those from other countries discussed in detail elsewhere¹⁷ should be revised. New guidelines should incorporate the principles of cost-effectiveness, an approach studied by Winkelmayr and colleagues¹⁸ and applied with much success by the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom.

The higher rate of stroke and thromboembolic events and possibly a higher risk for cancer in TREAT with only very modest benefits to quality of life tip the scale in favor of no ESA treatment of anemia in most nondialysis patients with CKD. Consequently, the best evidence we have so far supports holding off on ESA treatment for the majority of nondialysis patients who have CKD with anemia (National Kidney Foundation definition of anemia: adult males <13.5 g/dL and adult females <12.0 g/dL¹⁶), unless there are extenuating circumstances. A tradeoff of higher risk *versus* reduced blood transfusions is an alternative; however, this strategy should be used selectively and after discussing risks and benefits with the patient.

In patients with mild to moderate anemia (Hb approximately 9 to 11 g/dl), especially those who feel well, or even those with mild symptoms and low-level fatigue, non-ESA-based strategies should be the focus of treatment. Iron therapy, the exclusion of occult bleeding, and suppression of any inflammation (*e.g.*, an infected ulcer in a patient with diabetes) should be the focus. At

least for the first 3 mo of anemia management, iron therapy with oral iron should be tried; only if unsuccessful should intravenous iron therapy be attempted. Long-term safety studies in nondialysis patients who have CKD and are treated with intravenous iron have not been done; therefore, we should use iron products with caution. A blood transfusion or treatment with a short course of ESA may be necessary as “rescue therapy” for patients who have CKD with anemia and anemia worsens (Hb <9 g/dl) and the patient becomes symptomatic. In patients with a history of cancer or those who are undergoing chemotherapy, there should be a very high threshold for use of ESAs, even among patients who are symptomatic. Data from TREAT support such an approach, as do data from the cancer literature.¹⁹ Most patients who have cancer with CKD should be treated with blood transfusions, not ESAs.

In patients who are transplant candidates or have more severe anemia (Hb <9 g/dl) and cannot be managed with regular blood transfusions, long-term treatment with ESAs should be considered. It is likely, on the basis of the TREAT experience, for many patients, dosages of 500 to 1000 U/wk epoetin-alfa (or its equivalent in darbepoetin) will be sufficient to maintain Hb in the 9- to 11-g/dl range, but it is likely these patients will be at risk for needing blood transfusions. For patients for whom blood transfusions are contraindicated (e.g., transplant candidates), higher ESA dosages may be necessary to achieve Hb levels in the 9- to 11-g/dl range, but the dosage of ESAs should be moderate (<5000 U per week or equivalent of epoetin).

In conclusion, avoiding use of ESAs in managing anemia in nondialysis patients with CKD is now the soundest approach given the remarkable observations from the TREAT study. Is this a major shift in managing CKD anemia? Yes, but this is precisely why expensive randomized clinical trials are undertaken. These trials represent type A evidence. Are more trials necessary? Absolutely. Important questions remain unanswered. For example, are ESA-hyporesponsive patients with inflammation at greater risk? Is there a similar risk in dialysis patients with CKD? Is there a toxic dosage range for ESAs? Is there an ESA class effect? Does frequency of ESA administration make a difference? Is stimulating endogenous erythropoietin production using a HIF-1-stabilizing agent safer than using an exogenous recombinant ESA? Turning back to Dickens,²⁰ quoting from his book *Hard Times*, he counseled, “There is a wisdom of the head, and a wisdom of the heart.” On the basis of the results of the TREAT study and the CHOIR and CREATE studies preceding it, the time has come with respect to ESA treatment of nondialysis patients with CKD for “a wisdom of the head.”

DISCLOSURES

A.K.S. was principal investigator of the CHOIR study and a member of the executive committee for the TREAT study, and has received consulting fees from Ortho Biotech Clinical Affairs/Johnson & Johnson, Fibrogen, Amgen, Roche, and Watson and lecture fees from Ortho Biotech Clinical Affairs/Johnson & Johnson, Roche, Amgen and Watson; has served on advisory boards for Ortho Biotech Clinical Affairs, Roche, Watson, AMAG, and Amgen; and has received grant sup-

port from Ortho Biotech Clinical Affairs, Roche, Watson, Johnson & Johnson, AMAG, and Amgen.

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Staying on Top of Things Right from the Start: The Obsessive-Compulsive Disorder of Regulatory T Cells

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Our choice of partners, so they say, is subconsciously directed by an immune system aiming to making itself more diverse and robust. This strategy seems to work quite well if one looks at the highly complex structures that underlie human immunology, which still surprises with unexpected enigmas even after decades of intense research. Another recent proof of this phenomena is the study by Eller *et al.*¹ in this issue of *JASN* that describes a surprisingly aggravated course of glomerulonephritis in mice lacking the chemokine receptor CCR7.

The family of chemokines and their receptors are important mediators of directional leukocyte trafficking under inflammatory and homeostatic conditions. Given the complexity of the immune system and the multitude of different leukocytes, guidance by the chemokine family is much needed to facilitate the interaction of the right leukocyte subsets at the right time and in the right location. CCR7 is particularly crucial in the initiation of antigen-specific immune responses.²

Upon encountering a danger signal, antigen-bearing dendritic

cells upregulate CCR7 and become responsive to the corresponding ligands CCL19 and CCL21, which are expressed in secondary lymphoid organs. Likewise, naive T helper cells bear CCR7 on their surface and are similarly directed to lymph nodes and spleen. Here, these two cell types interact in a favorable environment to initiate a T cell response.

Given that Eller's nephrotoxic nephritis (NTS) model of glomerulonephritis is strongly T cell dependent, one would assume that interference with this CCR7-mediated T cell activation pathway might result in amelioration of disease; it did not. To understand why, it is necessary to look further at recently identified functions of CCR7.

First, the groups of Butcher and Luster^{3,4} convincingly showed in the past few years that CCR7 is involved in the egress of T cells from peripheral tissues; therefore, lack of CCR7 might result in the renal accumulation of T cells that have entered the kidney and no longer can leave in an orchestrated manner. Indeed, spontaneous lymphocyte accumulation and subsequent tissue injury are reported in several organs in CCR7-deficient mice.⁵

Second, Schneider *et al.*⁶ reported yet another function for CCR7. They showed that not only effector T cells but also regulatory T cells (Treg) need this receptor to be guided to sites of antigen-specific activation. Lack of CCR7 resulted in exacerbated experimental colitis, demonstrating that activation of effector T cells was achieved by alternative mechanisms. On the contrary, effector T cell suppression by Tregs was insufficient, suggesting dependence of this process on CCR7.

Eller *et al.*¹ further underscore the importance of these findings in their current article. Having already demonstrated some years ago that Tregs ameliorate the kidney-directed immune response in the NTS model,⁷ they now show that lymph nodes and spleens of nephritic CCR7 null mice contain significantly fewer Tregs than those of wild-type controls. Importantly, adoptive transfer of CCR7⁺ Tregs into CCR7 null mice restores Treg numbers in lymphoid organs and ameliorates disease, whereas transfer of Tregs from CCR7 null mice does not.

These findings once more highlight the potential role of Tregs as therapeutic targets in autoimmune disease and make them a rewarding subject to study. Two very important aspects of their biology are how and where they exert their anti-inflammatory actions.⁸ It has become evident over the past few years that Tregs are by no means a singular population; to the contrary, they form many different subsets.⁹ Each of these subsets seems tailor-made for suppression of a distinct type of immune response. In analogy to the development of Th1, Th2, or Th17 helper responses, corresponding Treg populations expand concordantly. How closely related these two counterregulatory arms of the immune response are is highlighted by the fact that programming of lineage-specific T effector and T regulatory responses relies on several of the same key transcription factors.^{10–12}

This is an arrangement, like most biologic processes, that makes perfect sense. Tregs need to be present at the site of ongoing immune responses to exert their anti-inflammatory actions; therefore, they need similar properties and trafficking receptors as effector cells. It has indeed been shown that lineage-specific che-

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