NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

Novel Therapies to Enhance Survival

Workshop on Inflammation in ESRD Patients

April 21–22, 2010
Bethesda, MD

MEETING OBJECTIVES

More than 400,000 people are currently treated by hemodialysis (HD) under the auspices of the U.S. End-stage Renal Disease (ESRD) program. The mortality in this group of patients is unacceptably high. Many mortality risk factors, such as age, gender, ethnic background, and presence of diabetes are not modifiable. A majority of the deaths are due to cardiovascular diseases, followed by infectious complications and malnutrition. Strategies to reduce the mortality of patients, including those directed at cardiovascular risk factors, have largely been ineffective.

Inflammation has been implicated in the pathogenesis of atherosclerotic cardiovascular disease, as well as malnutrition, and has been shown, using diverse measures, to be linked to increased mortality in HD patients for more than a decade. The majority of the data come from observational studies. Therapeutic interventions, such as biologic interventions directed against dysregulation of cytokine biology, however, have not been tested in large randomized controlled trials in the ESRD population. The benefits and adverse consequences of combined anti-inflammatory therapies are unknown, and need to be tested in diverse patient groups before large randomized controlled trials can be initiated. Perhaps because of the redundancy and pleiotropy of the inflammatory response multiple interventions will be required, but there are concerns regarding adverse effects with such strategies. There is, however, potential for public/private collaboration in such studies.

The NIDDK-sponsored workshop, Novel Therapies to Enhance ESRD Patient Survival, developed with collaboration from the National Institute of Arthritis and Musculoskeletal Disorders, addressed inflammation and anti-inflammatory cytokine responses, malnutrition, and cardiovascular disease in the context of ESRD patient morbidity and mortality. The focus was on ESRD HD patients, because of the nature of the previous literature. The workshop facilitated discussions of the types of research necessary to advance the field, a hierarchy of interventions, and considered the number of subjects necessary for effective trials. In addition, discussions took place regarding finding the proper balance between and timing of proposed pilot and feasibility studies and definitive trials in this field.

MEETING SUMMARY

The workshop involved NIH personnel, academic scientists and clinicians engaged in inflammation research from outside the field of nephrology, nephrologists interested in inflammation, clinical trials science and patient care, representatives from the Food and Drug Administration and industry leaders. The workshop included lessons learned from previous trials of anti-cytokine therapies and challenges encountered in clinical trial design. Clinical and basic scientists presented their experiences and views on studies in patients with systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis and psoriasis, as well as in ESRD patients. Previous clinical trials of anti-cytokine therapies in non-nephrology patients were reviewed. A plenary talk was given on the interrelationships of proinflammatory and anti-inflammatory mediators during clinical interventions. A FDA representative presented an overview of adverse events in trials of anti-cytokine therapy in non-nephrology patients. Speakers from eight companies gave presentations at an Industry Round Table related to anti-inflammatory therapeutics.

These presentations were followed by breakout sessions which included all meeting attendees. The breakout groups were tasked with answering questions regarding adverse events and pilot and feasibility issues, issues related to the use of combination therapies in ESRD patients, patient selection, sample size and inclusion/exclusion criteria in studies of anti-inflammatory therapies in ESRD patients, and qualification of biomarkers. Breakout group presentations were followed by open discussions.

REPORTS FROM BREAKOUT GROUPS

Specific questions were addressed to each of the workshop groups.

GROUP A: ADVERSE EVENTS/PILOT AND FEASIBILITY ISSUES

Group A addressed pilot and feasibility issues and potential adverse events in planning trials to treat inflammation in ESRD patients.

Question 1: Should anti-cytokine therapy be evaluated in ESRD patients? Should there be more rigorous pre-clinical data to provide a rationale for clinical investigation?

The group felt Phase I studies in ESRD HD patients were potentially important. Single agents as well as multiple agents (anti-TNF-α, IL-1, IL-6) could be evaluated in ESRD HD patients. Studies could be of relatively short duration, and might focus on interdialytic and intradialytic pharmacokinetics. Goals would be to assess major toxicities and gain information regarding possible study confounders. Phase II targets might be endpoints associated with nutritional status, responsiveness to erythropoietin-stimulating agents (ESAs) and assessment of changes in putative biomarkers.

Question 2: What information is needed regarding adverse events to inform planning of pilot and feasibility trials of anti-cytokine therapies in ESRD HD patients?

More information is needed on anti-cytokine therapies in other illnesses, such as rheumatoid arthritis and inflammatory bowel disease, coupled with risk data on medical problems in HD patients. Preliminary estimates will need to be made, and inferences will be drawn on how similar ESRD patients are to other patients who have undergone such therapies.

Question 3: What are the risk/benefit balances of anti-cytokine interventions? How will assessments differ in pilot and feasibility and definitive outcome studies?

The group felt infection would be a frequent complication of anti-cytokine therapy in ESRD patients. Quantification of infection risk is currently difficult, especially since length and type of therapy, doses of drugs (duration and intensity of treatment) and endpoints to be assessed are unclear. It is currently premature to plan details of definitive outcome studies, but planning of pilot and feasibility studies will include parameters which will most probably be assessed in definitive studies (including quality of life, physical function, and/or end-organ functional changes).

Question 4: What are the characteristics of ESRD patients who will be selected for pilot and feasibility anti-cytokine trials?

In principle patients should be selected who would have minimal risks receiving anti-cytokine interventions, but potential measurable benefits. Generalizability will be a question regarding the patients recruited to participate in pilot and feasibility studies. Prevalent HD patients with a native AV fistula (with diverse underlying diseases) should participate.

Patients should be relatively healthy and free of obvious contraindications. Those with active infections, uncontrolled diabetes, recurrent sepsis, active tuberculosis (TB), hepatitis B/C, HIV, melanoma, lymphoma, demyelinating disease, active systemic lupus erythematosus, central catheters, or Class III/IV CHF would be less suitable for such studies.

Patients with relatively high circulating C-reactive protein (CRP) levels might be valuable to include in pilot/feasibility studies in order to demonstrate potential treatment effects.

Question 5: What adverse events (AEs) and serious adverse events (SAEs) should be expected and tolerated in pilot/feasibility studies of ERSD HD patients?

Careful monitoring, the collection of multiple clinical and laboratory safety measures, and Data and Safety Monitoring Board (DSMB) oversight will be essential in early studies. Safety monitoring would include at least assessing immediate allergic reactions, sepsis and serious infections, and other known adverse effects of individual therapies.

Question 6: What AEs and SAEs will be expected and should be tolerated in long-term outcome studies?

The working group felt such questions were premature in light of the present information base.

Question 7: How should stopping guidelines be used in pilot/feasibility studies?

The working group felt there were currently no pre-determined rules to guide stopping in such studies. Stopping a study will depend on the biomarker assessed, the safety of the intervention, the feasibility of achieving recruitment goals and will be up to DSMB discretion.

Discussion

The working group emphasized that anti-cytokine therapeutics differ, particularly regarding effects on binding and antibodies. The effect of a variety of agents on TNF-α, IL-1, and IL-20 biology in ESRD HD patients likely would differ. Trials should be designed individually and will differ across diseases and across agents given to patients with the same disease.

Data exist in preclinical animal models of anti-cytokine therapy. Animal models can be beneficial, but they should not be a prerequisite to Phase I human studies, if a rationale for treatment exists. The mouse can be useful to dissect potential therapeutic issues; however, the human is often quite different.

GROUP B: COMBINATION THERAPIES AND BIOLOGIC ISSUES

Group B addressed issues related to the use of multiple therapeutics administered simultaneously or sequentially and potential adverse events in planning trials to treat inflammation in ESRD patients.

Question 1: How should priorities be set for choosing individual anti-cytokine agents used in interventional studies in ESRD HD patients?

The working group felt the key priorities were: safety, followed by tolerability, feasibility, efficacy and cost. Availability of pre-clinical and Phase I data would be important for deciding which studies to implement first. Pharmacokinetic data regarding renal and dialytic clearance was felt to be important (dialyzable and/or non-renal clearance preferred).

Question 2: When and how should combination therapies be used in pilot and feasibility outcome studies?

Time frames for pilot and long-term studies were considered by the group. Single dose administration studies for safety, tolerability, and initial pharmacokinetic data were considered to be a high priority. 30-90 day studies would be suitable for establishing tolerability and proof of concept. Assessments of antibody development at a time greater than 90 days after drug discontinuation will be important. A 90-180 day time frame for studies will be useful to assess intermediate outcomes and feasibility. The working group felt it is premature to address long-term study designs.

Question 3: What are the barriers to using combination anti-cytokine therapies in ESRD HD patients?

The working group was concerned regarding the safety of dual or multiple anti-cytokine therapies, especially as initial studies. Data regarding infections from studies of anti-cytokine therapies in patients with rheumatoid arthritis suggest caution should guide combination approaches initially. The working group saw possible value in alternative approaches, using adjunctive therapies, for example considering pilot studies of statins plus anti-cytokine therapy**,** as well as combinations of anti-cytokine therapies and anti-oxidants, vitamin D preparations, phosphate binders, or renin-angiotensin-aldosterone system (RAAS) inhibitors.

Question 4: What priorities should pilot and feasibility studies of anti-cytokine therapies for ESRD HD patients have?

The working group felt such studies should have “very high priority,” since there are few proven therapies which are beneficial in ESRD, chronic kidney disease (CKD) is increasing in prevalence in the United States and worldwide, and robust epidemiologic data exist associating inflammation with adverse outcomes in ESRD patients.

In addition, therapy of kidney disease-related inflammation provides a testable hypothesis with strong biological rationale. Possible pleiotrophic beneficial effects can be conjectured from anti-proinflammatory cytokine therapy in ESRD HD patients. The possibility of public-private partnerships is a potential opportunity for such studies.

The group felt anti-inflammatory interventions for ESRD HD patients in the very near future were feasible and important, and were of potentially high priority, in spite of limited data in CKD and ESRD patients. Collaborative networks and small and large investigator-initiated studies will be necessary to move the field forward.

Discussion

The breakout group felt that dose escalation studies (pharmacokinetic and pharmacodynamic studies) were important to plan. The group felt relatively high doses will likely be needed to achieve desired effects in target populations. The breakout group felt less, rather than more complex trial designs would be useful at this time.

The breakout group focused on the length of pilot studies and did not consider exclusion criteria. The endpoints suggested are exploratory. Comparisons (e.g., quality of life, clinical endpoints) should be developed during a more in-depth design process. An organ-related endpoint would be worthwhile. Exploratory endpoints could include biomarkers of oxidative stress as well as circulating cytokine levels. Data should be collected in a variety of different domains. Assessing the effects of anti-inflammatory therapies on proinflammatory as well as anti-inflammatory mediators will be important.

Measures should focus on parameters which are well-understood. For example, a trial might measure circulating biochemical parameters and biomarkers rather than hard clinical outcomes.

GROUP C: PATIENT SELECTION—INCLUSION/EXCLUSION CRITERIA

Group C addressed patient selection and inclusion / exclusion criteria in planning trials to treat inflammation in ESRD HD patients.

The number of randomized controlled trials (RCT) published in nephrology and 12 other specialties of internal medicine from 1966 to 2002 has been documented and published in the *Journal of the American Society of Nephrology*. The lowest number of RCTs are in the field of kidney disease.

The working group envisioned short-term (90 day) pilot studies of anti-cytokine therapies. Placebo-controlled designs, with monthly physical examinations and blood work, and frequent safety follow-ups would be most appropriate for such studies.

Question 1: What data do we need regarding patient selection criteria for studies of anti-inflammatory therapies in ESRD HD patients?

Information must be collected regarding age, gender, etiology of ESRD, dialysis modality, time on dialysis, and vascular access history. Additional information regarding previous transplantation and administration of immunomodulatory therapies would be important. History of malignancy and genetic kidney disease may be useful to guide inclusion and exclusion criteria. Records should be kept regarding socioeconomic status of study participants.

Question 2: Which patients should be selected?

Exclusions should consist of patients with prior organ transplantion, history of recent myocardial infarction or stroke or autoimmune systemic diseases. Patients should have no active or recurrent infection, and no evidence of malnutrition or wasting (e.g. 10% weight loss over 90 days, serum albumin concentration [SAlb] less than 3.5 g/dL, body mass index [BMI] < 20). Patients included in studies should not have dialysis central venous catheters. Patients selected for anti-cytokine therapeutic trials should have been previously adherent to their dialysis prescription and should have no uncontrolled co-morbid conditions.

Question 3: What should be the clinical characteristics of participants?

Studies should enroll stable patients with adequate dialysis (average spKt/V > 1.2 over 3 months), with no evidence of active immunologic disease, with controlled co-morbid conditions (e.g. diabetes, hypertension), stable nutritional status and well-controlled calcium, phosphorus, and PTH levels.

Question 4: What should the primary outcomes be in studies of anti-inflammatory therapies in ESRD HD patients?

Primary outcomes, in addition to levels of circulating cytokines, could include markers of endothelial function. These might include platelet activation markers, such as P-selectin, and leukocyte activation markers (L-selectin), as well as markers such as sICAM I, sVCAM, sE-selectin, and asymmetric dimethyl arginine (ADMA).

Question 5: What should the secondary outcomes be?

Changes in baseline sAlb, dietary intake, and weight gain; improved anemia management and/or responsiveness to ESAs; improved calcium, phosphorus, and PTH levels; quality of life assessments; and other surrogate biomarkers (suggested by the Biomarker breakout group).

Question 6: How should we power analyses?

We need to develop studies of the relevant biomarkers and their changes over time in the pertinent patient populations. In addition, we need to understand the impact of the variability of the selected endpoints over time. More information is therefore necessary to allow us to provide accurate, meaningful power estimates.

Question 7: What should we expect and tolerate regarding adverse events in studies of anti-inflammatory therapies in ESRD HD patients?

An ideal therapy would result in no increase in infections or sepsis compared with placebo groups, no increase in venous thrombosis, or other cardiovascular events compared with placebo groups, and no worsening of baseline measurements compared with placebo groups. In long-term followup, there should be no increase in malignancies, infections or recrudescence of latent infections (TB, cytomegalovirus infection) compared with control groups.

Discussion

The breakout group discussed an absolute safety study and exactly which patients to consider. The group did not reach a consensus about this. The breakout group advocated an "ideal" set of patients. The appropriate patients for an ESRD trial rather might be those who have muscle breakdown or who have high levels of inflammatory markers.

The breakout group felt that patients should have no evidence of malnutrition/wasting. It was pointed out that weight loss may help to reduce inflammation. A controversy exists about how much of the decrease in sAlb is caused by inflammation.

Caution should be exercised regarding how calcium, phosphorus, and high PTH levels are defined, as their rates may differ by population.

A decrease in CRP does not necessarily correlate with how well a subject responds to an agent. CRP levels can change dramatically in a substantial proportion of patients over a few days. CRP data should be interpreted cautiously. Its half life is variably 7 to 10 days (up to 3 weeks), with clinical effects apparent in 1 week. Because some mediators affect IL-8 without changing CRP or IL-6, CRP should not be used as a primary outcome measure. The magnitude of changes and variability over time in markers are often easier to evaluate in autoimmune populations.

In pediatric trials sponsored by industry, markers of resistance have been found. Subjects with impaired bone growth may not respond in the same way as other patients.

The working group suggested minimizing adverse events and desired to minimize infections, with proposed interventions. The potential benefits of anti-inflammatory drug trials in ESRD patients include a decrease in long-term mortality. If patient survival improves, adverse events may be tolerated. Few patients, however, will prefer important risks in exchange for small changes in short-term mortality. Bone mineral metablolic parameters could serve as tenable short-term markers while long-term studies are being planned.

The breakout group did not focus on specific subgroups, such as pediatric ESRD patients. Diseases in children are antecedents of adult disease, and growth responsiveness should be examined in pediatric ESRD patients. Assessment of neurocognitive as well as physiological development should be considered. The pediatric patient is the “pure” patient because of the lack of comorbidities in this population. The pediatric population should be included in trial designs.

GROUP D: BIOMARKER/SURROGATE MARKERS

Group D addressed the role of biomarkers in planning trials to treat inflammation in ESRD patients.

Question 1: What are the proper biomarkers to be used in pilot/feasibility studies?

The working group addressed several goals for biomarkers in studies of anti-inflammatory therapies for ESRD HD patients.

Safety was thought to be likely specific for an individual therapy. It would be desirable for studies to demonstrate proof of activity. In other words, studies should be designed to demonstrate that the therapy has its intended biologic effect (for instance, a decrease in signaling for a specific cytokine). These determinations will also likely be specific for individual therapies.

Factors contributing to inflammation in ESRD patients potentially include uremic toxins (related to loss of kidney function), oxidative stress (related to insulin resistance), comorbidities (atherosclerosis, diabetes mellitus, infections, etc), and consequences of the renal replacement therapy itself (such as generation of endotoxins, consequences of bioincompatibility, and comorbidity related to vascular access).

There currently exist insufficient data on the natural history of biomarkers (excluding serum albumin concentration [SAlb]) in the ESRD HD population. This field is an exciting opportunity for future research.

Cross-sectional studies of inflammatory biomarkers in a CKD-ESRD population would be of substantial value for the design of pilot studies. Such studies might consider the causes of CKD (eg diabetes mellitus or hypertension). There may be advantages to studying uniform populations as well.

Biosamples could be analyzed using techniques including: FACS analyses, RNA profiling, and analyses of serum and urine proteins, muscle, adipose tissue, and DNA. Imaging modalities have the potential to elucidate bone mineral metabolic and endothelial responses to therapies.

Study periods could consider pre-initiation, initiation, and 3 month followup groups, using paired sample analyses. Pilot studies might be necessary to help estimate adequate sample sizes.

Such studies could represent starting points for industry/academic partnership. Pilot studies should have a wide spectrum of patient participants and outcome assessments, including measurement of several classes of biomarkers.

Biomarker classes to consider would include

- CRP, SAlb
- Cytokines: IL-6, IL-8, IL-10
- Adhesion molecules: VCAM, P-selectin, E-selectin, fibronectin
- Endothelial markers: VEGF
- Oxidative stress markers
- Iron studies: hepcidin, ferritin
- T cell subsets, NK cells
- Serum amyloid protein A, gelsolin

Question 2: What are the proper surrogate markers to use in pilot/feasibility studies?

Markers will vary according to the endpoints assessed. Markers will differ if defined endpoints capture mortality versus CV events versus changes in perceived quality of life. It should be noted that even for diseases where there are "accepted" surrogates (e.g., cardiovascular disease), it is unclear if the same surrogates are acceptable and function in similar manners in ESRD patients. For mortality, there are no clear surrogates.

Pilot studies should therefore explore several easily measurable clinical variables that are associated with mortality, and consider the biological plausibility of a particular therapy affecting outcomes of interest.

Clinical markers to consider include:

- Weight loss/change in BMI
- Response to ESAs
- Hyponatremia
- Decrease in SAlb
- Periodontal disease
- Fatigue/depression
- Peripheral arterial tonometry
- Indices of bone disease

A "Kidney Disease Activity Index" might be an attractive parameter that would provide uniformity in assessment in various studies of diverse interventions. Endpoint selection will be the first consideration, but the target patient population (eg advanced CKD vs. ESRD) will also entail limits to the development of an appropriate composite outcome. A combination of objective outcomes and patient-oriented outcomes is appealing. Investigators would need to work closely with the FDA to ensure that such an index could be used in the process of qualification.

Question 3: Will biomarkers used vary for pilot/feasibility studies and definitive outcome studies?

No — the goals for the use of biomarkers are the same. On the other hand, the scope of possible parameters to be assessed will be wider in pilot/feasibility studies. Final measures can be tailored based on the specific intervention in definitive outcome studies.

Question 4: What should be the time frames using biomarkers in pilot studies and definitive studies?

A key consideration is the tissue target and potential response time of target tissue (eg muscle vs. bone). Possible targets include muscle mass (aldolase, creatinine), bone metabolism and erythropoeisis. These considerations also apply to power calculations for such studies.

Questions 5: How will power be assessed in pilot studies and definitive studies?

Pilot studies are for signal generation, and do not need to be "confirmed" by a strict p value of 0.05. We need better data for intermediate outcomes for such studies with an eventual goal of qualification.

Discussion

The length of time it takes for a drug to affect muscle mass will affect the length of the pilot project. If an agent takes 3 months to affect muscle mass, then the pilot must be designed with at least a 3 to 6 month time frame. A shorter pilot could be conducted if the agent has quicker effects. Designs of pilot studies could include broad data collection to facilitate generation of hypotheses.

The breakout group discussed how to measure biomarkers and the need to understand confounders and mechanisms of action as well as the relevance of putative circulating biomarker levels. One possible design is to conduct a direct assay in a small number of ESRD patients, focusing on subclinical inflammatory myopathy. This approach focuses on tissue responses, and would evaluate long-, medium-, or short-term time frames. Designs focusing on the vasculature might determine effects on intimal medial thickness or vascular rigidity over 3 to 6 months. Bone studies might integrate the effects of inflammation over time.

Determining the outcomes for the long-, mid- and short-term assessments of the tissue being evaluated might help with determination of drug dosage levels to be used in pilot/feasibility studies. Adipose tissue should be considered as an endocrine organ and evaluated for its role in inflammatory pathways.

Creatinine should be measured in muscle biopsies as a measure of inflammation, along with more traditional measures of muscle power and muscle volume. Evaluations of musculature could be accomplished via either imaging studies or physical measurements — such as MRI evaluations or simple strength measurements.

The breakout group initially started discussing studies with the ESRD population and shifted to patients in transition from CKD to ESRD. A presample might yield understanding of how patients change as they move from late stage CKD to being on dialysis. Challenges include how to predict which patients will start dialysis earlier and when patients will need to start dialysis.

A study of relatively unselected patients with a fairly high event (mortality) rate who are evaluated over time would provide natural history data that currently are lacking.

The breakout group's proposed trial started as a longitudinal study. This could be refined to obtain focused data at a number of time points. Because of the number of biomarkers that might be involved, the number of patients may be an issue.

The idea of the cross-sectional study was to examine patients before they started dialysis and immediately after they started dialysis. The information gained could be used to conduct a longitudinal study.

The breakout group suggested determining the inflammatory profile of tissues in addition to that of the circulation might lead to broadening the potential scope of research initiatives.

The group noted there is a substantial proportion of people with CKD stages 3 and 4 who do not progress, compared with the relatively small number who progress to ESRD. Such differences can be used to characterize outcomes, but uncertainty in prediction would increase the number of subjects needed in both pilot and definitive studies.

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