



THE TARGET

TARGETING ACUTE LIVER FAILURE TO FIND A CURE IN THE 21ST CENTURY

A Word from the PI . . .

Reviewing the Sixth Annual ALF Meeting

Another year has rolled by, and another successful meeting at Dallas/Fort Worth International Airport has come and gone. This year's meeting was the sixth for the group, and our largest to date. What did we learn at that meeting?

First, we learned that the Acute Liver Failure Study has continued to grow, with 25 active adult sites and 23 active pediatric sites. The pediatricians, under Rob Squires' able guidance, have gone international, bringing in clinical sites from Toronto, Canada, Birmingham and London in the United Kingdom. The number of cases in the adult registry has exceeded 500, with Northwestern adding the 500th case. Pediatric registry cases now exceed 150. It is a tribute to all of you, who day after day, case by case, work to see this study evolve and succeed. And my thanks to all of you who took time to come to the meeting.

Next, we learned that the NAC study continues to enroll patients; now we are up to 60 on our way to 200. Julie Polson summarized the results. Of course, there are no overall therapy results to disclose because we will remain blinded until the study is completed. Nevertheless, she emphasized the importance of this study, its rationale and the inclusion/exclusion criteria. We are committed to finishing this study and want as many patients as possible enrolled. However, we caution you to be careful in choosing patients for enrollment. Patients with shock liver, acetaminophen even vaguely in the background, and those who are terminal and on pressors for that reason are not suitable. So keep the NAC cases coming. We need four cases per month and we are hovering at that level, but just barely. Let us know what we can do to help. With the shipment of this issue of *The Target* you should also be receiving plastic cards featuring my phone number day or night. I am happy to help with questions of suitability or other issues surrounding patient enrollment.

Below: Dr. Lee (Study Principal Investigator) discusses TPO, Gc Studies, and DNA Samples during the ALF meeting.



Several reports that followed Julie and Rob Squires were related to ancillary studies, mainly works in progress. Ray Chung and Mike Schilsky have long term projects under way to examine the role of cytokines and heavy metals in patients with acute liver failure. Bob Brown, in addition to providing us a digital camera for the group photo, spoke about the role and limitations of living related donors in regard to acute liver failure, and Rick Paules, from the National Institute of Environmental Sciences, spoke about their program developing microarray technology to identify drug-related liver injury.

The remainder of the meeting was largely spent in reviewing procedures and problems, and in committee meetings. The pediatric group met as a committee of the whole to fine tune the NAC protocol. The adult group committees, including steering, serum bank, ancillary studies and marketing, all were able to meet. A separate report of the committees, developed by Julie Polson, appears on pages 2 and 3.

All in all, it was a highly successful meeting. We have two aims for these meetings: Learn something new about ALF, and update you on study procedures, plans and challenges for the coming year. I think we were able to fulfill these goals.

We welcome your suggestions for improving this meeting, and improving any aspect of the group or the process by which we govern ourselves. Just drop me a line by email at William.Lee@UTSouthwestern.edu, and I will respond promptly. Remember, this is YOUR study!



Investigators and Coordinators photo taken during the adult breakout session at 2002 annual ALF December meeting.

Another Big Success for ALFSG Annual Meeting by Julie Polson, M.D.

As 2002 drew to a close, the group reached an important milestone: we now have over 500 cases in the registry! (Exact tally: 543). We currently have 22 active adult sites (congratulations to recently IRB-approved Mayo-Jacksonville), and look forward to the addition of University of Medicine and Dentistry New Jersey, Colorado, Duke, and South Carolina, who currently await approval to begin enrollment. We have several ancillary studies under way, and continue adding to the list of ALFSG publications. (Look for reprints of the Ostapowicz, et al paper from the Dec. 17 edition of *Annals of Internal Medicine*).

While the registry continues to accumulate valuable data, we cannot forget our aim of testing intravenous N-acetylcysteine in patients with ALF for whom no specific treatment is available. We need to enroll 200 patients in the NAC trial by September of 2005, and with our current total of 56, we are decidedly behind the curve. While DSMB members at the most recent meeting voted unanimously to continue the trial, the group did offer a few suggestions. Their biggest concern was enrollment. They also suggested greater efforts to capture missing data, and stressed the importance of including details regarding transplant eligibility. NAC enrollment had picked up during the fall months, but has not been optimal in December and January (two cases in each of those months). We need at least four to five NAC cases every month now in order to reach our goal sample size by the end of the grant. This trial is of key importance, and therefore NAC recruitment must be our major mission for 2003.



Figure 1 - NAC enrollment for 2002.



Figure 2 - NAC enrollment 1998 to present.

Committees

by Julie Polson, M.D., William M. Lee, M.D. & Robert Fontana, M.D.

Recruitment Committee:

It is clear that recruitment continues to be an issue of utmost importance, particularly as far as the NAC trial is concerned. We have therefore formed a committee of highly motivated ALFSG members whose responsibility it will be to promote patient recruitment and maintain group energy in terms of enrollment. Dr. Lorenzo Rossaro, whose site (University of California at Davis) has recently turned in stellar numbers, will serve as committee chair. The committee's first gathering at the December meeting in Dallas generated ideas about increasing general awareness of the study in order to minimize potential for "missed" cases. Of utmost importance is each site's responsibility to inform and educate its house staff, fellows, faculty, and other hospital staff about the study. In addition, there must be a publicized procedure whereby study personnel can be expeditiously contacted for questions or notification of potential cases. We also considered possible ways in which to improve success with obtaining consent. Several suggestions for achieving these goals were discussed, and will be available in more detail in the Committee Report to be sent out shortly. All in all, the first meet-

ing of the Recruitment Committee was full of lively discussion and idea generation. The committee takes its role in the ALFSG very seriously and looks forward to working with all involved to help maintain and hopefully increase our enrollment as we continue to target ALF in 2003 and beyond!

Publications Committee:

The Publications Committee has the responsibility of reviewing all manuscripts and abstracts as well as formal presentations concerning the ALF study. It is important that we continue to publish and present our data, and it is crucial to have a review process in place to ensure that the ALFSG continues to put forth high quality product, which will help the medical community gain a better understanding of acute liver failure. Abstracts and manuscripts should be sent to the committee for review prior to submission to journals or conferences. The committee wishes to make itself available for consultation at all stages of the authorship process, from help with concept development to decisions regarding submission. In order to facilitate organization and standardization of the publication process, we will begin keeping a log of submission/publications. A work may be entered as early as the concept stage, and comments made during different stages of review can be kept in the log to track the development of ideas/manuscripts. A list of ALFSG publications, including recent abstracts and forthcoming publications, was included in the handbook for the December 2002 ALFSG Meeting. If you do not have this list, one can be sent to you. The committee will maintain and continue to update the list periodically, and will make this list available to the group at large.

Serum Bank Committee:

The serum bank at UT Southwestern continues to provide valuable material for use in several ALF ancillary studies. In the past few months we have supplied sera for ongoing investigative efforts in such areas as HBV core promoter mutations, APAP adducts, apoptotic markers, hepatitis E virus, and Parvovirus B 19, and several other proposals are currently under review.

The Serum Bank Committee will evaluate all requests for sera in order to help ensure that samples are distributed and utilized appropriately. Proposals (including documentation of the study's purpose, planned methods, and amount of serum needed) should be submitted to the committee for consideration after approval

by the Ancillary Studies Committee. Sera will be shipped only after both committees have approved a proposal.

The staff at UTSouthwestern is currently working on updating a log of serum samples in order to make the process more efficient. It is important that all sites continue making every effort to collect adequate samples on enrolled patients. Remember to label all samples with permanent marker before shipping to the central site.

(More on Committess on Page 6)

Housekeeping Issues

by Ezmina Lalani

We would like to thank everyone who attended the sixth annual ALFSG meeting. We hope the experience was both educational and enjoyable. Many of the study housekeeping issues were discussed during the breakout sessions. We are requesting all sites to fax their initial and continuing IRB approvals for NAC, LTFU, and DNA to the central site, UTSouthwestern. There are still a few sites that have not submitted the amendments from December 2001. Please get these amendments in as soon as possible, so all the sites can be fully on board. Each site is encouraged to completely fill out the admissions and outcome forms with a value or indicate "unknown". Please do not keep any part of the



The adult breakout session.

form blank. Sites have indicated they prefer having their own shipping boxes. All sites should have their own shipping boxes by February. This will make it easier to ship sera on an ongoing basis. Remember, once we receive the CRF, queries, and sera, we will accept invoices for enrolled patients. The central site will send out quarterly reminders to sites regarding their first year and second year follow-up patients. If you cannot contact a follow-up patient, please send the central site documentation of contact. Please contact the central site, if you have any questions or concerns regarding the study.

(More on Housekeeping on Page 7)

Notes from the Pediatric Breakout Session

by Robert Squires, M.D.

PEDIATRIC NAC PROTOCOL FINALIZED

The Pediatric NAC Protocol received its endorsement from the Data Safety and Monitoring Board (DSMB) was approved by the IRB at UT Southwestern. Details of the protocol were reviewed and discussed at the December meeting. Each site received a copy of the Protocol and Project Manual. We hope that as many sites as possible will seek local IRB approval and become actively involved with the NAC study. To remind you, each site will receive \$1,800 for each patient enrolled in the NAC study. This will be in addition to the \$500 for each patient enrolled in the Registry. We look forward to initiating this study the first quarter of 2003.

PUBLICATIONS

The consensus of those at the meeting was to write the first "overall" experience when we have complete data on 150 patients. Currently, we have data on 139, so we are close. Our third abstract entitled "Encephalopathy at presentation predicts outcome for children with acute liver failure" received a Presidents Choice Award at the recent AASLD meeting in Boston.

COMMITTEES

The pediatric investigators established several working groups to ensure consistent definitions throughout the study. The Infectious Disease Committee (Martin Martin, M.D., Chair) will help define when an infectious agent is a likely cause of the liver dysfunction. The Metabolic Disease Committee (Mike Narkewicz, M.D., Chair) is working on criteria necessary to confirm a particular metabolic defect. A Committee on Long Term Outcomes (Karen Murray, M.D., Chair) will develop a protocol and data collection form to follow children who survive beyond three weeks and either succumb to their illness or survive without a liver transplant. The SPLIT database should acquire data on those who receive a transplant. We continue to work on the minimum evaluation necessary to define a child with an "indeterminate" cause for ALF (Phil Rosenthal, M.D., Chair).

The growth of the study group has resulted in a need to form three new committees. One will oversee the serum bank, one will review ancillary studies and the third will oversee publications.

NAC Works!

(For Radio-Contrast Induced Renal Failure)

by William M. Lee, M.D.

A recent article in JAMA (Kay J, et al., Feb. 5, 2003;289:553-558) describes a randomized controlled trial of the safety and efficacy of N-acetylcysteine for prevention of radio-contrast induced renal failure in 200 Chinese patients. The results suggest that patients receiving NAC were protected from developing renal insufficiency. Twelve (12 percent) control and only four (four percent) treated patients increased their creatinine levels more than 25 percent from baseline in the study. No safety issues were discovered, although it should be stated that an oral dose was used. The current study, when coupled with an earlier pilot study that was reported in 2000 in *The New England Journal of Medicine*, also showing safety and efficacy, will have an important and widespread effect on clinical practice.

This new study suggests that there is value to NAC in another context than our own study. It serves as a reminder that NAC has utility, is being used elsewhere and that our study is important. We must seize our current opportunity to determine whether NAC is of value in ALF patients.

People ask me if they should use NAC in patients who might not qualify for our study (patients with shock, or patients at outlying hospitals with no funding). It is recommended not to use it, unless it can be used in the context of a trial, since there is no proof of efficacy at this point.



Pediatric investigators and coordinators who attended the December ALF meeting.



The pediatric breakout session.

Ancillary Studies in the Works

- Acetaminophen Adducts: This study is conducted by Tim Davern (UCSF PI) and Laura James, a pediatric gastroenterologist at University of Arkansas. Dr. James has an assay which detects acetaminophen bound to cell proteins in the serum of patients with acetaminophen poisoning. These adducts represent the smoke from the smoking gun. Understanding when adducts appear and disappear, and surveying sera from patients with indeterminate acute liver failure, are two important goals of this study.
- Serum Troponin Levels in ALF: Myocardial injury may occur in acute liver failure, particularly in association with acetaminophen poisoning. We at UTSouthwestern are using the serum bank to identify high troponin levels in patients with ALF, for further elucidation of the incidence and possible importance of myocardial injury in ALF.
- Prognostic Scoring System: Frank Schiødt and Linda Hynan, of UTSouthwestern's Academic Computing Department, are developing a new prognostic scoring system. Not so easy to do, but with the large numbers we now have in the study, we are cautiously optimistic that we can accomplish this goal.
- Treatment Protocol: Eileen Hay, Brendan McGuire, and Lorenzo Rossaro are undertaking a thorough review of the role of therapeutic options in ALF. For example, Eileen had shown that patients with acute liver failure survive longer if given lactulose, although overall outcome was not altered. This preliminary report, in abstract form, has led to a more detailed review of how we treat ALF. In addition to making inroads into understanding the role of treatment, Dr. Hay's committee hopes to develop a standardized protocol that all sites might consider adopting.
- Pathology of Acute Liver Failure: Drs. Lydia Petrovic and Hossein Saboorian from Mayo Clinic and UTSouthwestern, respectively, have expressed interest in reviewing all pathologic specimens available from the ALF Study to provide a comprehensive description of the pathology of this condition.
- Hepatitis E Virus in ALF: Dr. George Dawson from Abbott Labs, has undertaken a project to examine the role of hepatitis E virus in ALF cases, particularly focusing on the indeterminate group.
- Parvovirus B19: Drs. Neal Young and Kevin Brown at the National Heart, Lung, and Blood Institute, are testing a large number of sera for Parvovirus B19, the virus associated with many pediatric cases where aplastic anemia has been involved.

Where Are We Going with Drug Hepatotoxicity?

by William M. Lee, M.D.

There has been a lot of interest in drug-induced liver injury (DILI) in the last five years, perhaps in part due to the withdrawal of bromfenac and troglitazone by FDA for drug hepatotoxicity. Liver injury remains the number one reason for drug withdrawal in the United States and elsewhere. There have been several workshops sponsored by NIH, AASLD, FDA, and PhRMA, the pharmaceutical research and manufacturer's trade association in the past three years, and the US ALF Group's data has been key to defining the size of the problem. Clearly, if acetaminophen-induced cases make up 40 percent and idiosyncratic drugs another 12 percent to 15 percent of acute liver failure cases, this is a serious problem. NIDDK has proposed a multi-center group comprised of five sites around the United States, to gather information and important samples regarding drug-induced cases, particularly those related to idiosyncrasy with the aim of better understanding the pathogenesis of these severe liver injuries. Milder forms of liver damage would be considered, and it is estimated that only 12 percent to 15 percent of drug-induced liver injury reaches the threshold of acute liver failure.

Six sites in the ALF group began a study several years ago of what we called severe liver injury (SLI), cases with a wider definition than ALF. Rather than require encephalopathy, we focused on those patients admitted to study centers with an acute hepatitic illness who met the criteria of total bilirubin ≥ 10 mg/dL, or bilirubin ≥ 4 and INR ≥ 1.5 . This retrospective study of existing medical records relied on sites to identify patients using ICD 9 codes of all etiologies at first, but with the main focus being on the idiosyncratic cases. Of 307 patients identified, 61 (or 20 percent), were idiosyncratic DILI cases. These consisted of the usual suspects, NSAID's, antibiotics, (including isoniazid), phenytoin, disulfiram and herbs. We are still analyzing data from this study and a paper will be forthcoming. The criteria used in this study were probably not broad enough to capture most DILI cases, since we only found about 33 percent of cases that did not have encephalopathy, suggesting that we only picked up an additional 50 percent more cases by using the lowered criteria. Certainly in a study of this kind, no outpatients were identified. After the success of this retrospective study, a questionnaire was sent around to all ALF Study sites to gauge interest in a prospective study of this type. Fifteen sites responded, all positively. We have developed and are in the process of refining case report forms.

How do we move forward? This is the \$64,000 question. FDA would like to consider using the ALF Study Group sites for a prospective "real time" drug reporting system. However, several hurdles must be overcome. First, the NIDDK program is likely to overlap with our effort in several ways, and some of our study sites have sub-

mitted applications to become part of the NIDDK Network. Second, no funding mechanism is currently in place to support this study although two possible ones are in play. Finally, how would this drug alert network interface or dilute the effort we make in the acute liver failure study? It is flattering that FDA and PhRMA wish to work with us, but we need to work out the details of this potential alliance. UTSouthwestern will keep you posted and ask for your input regarding these issues.

Committees (Continued from page 3)

Ancillary Studies Committee:

The goals of the Ancillary Studies Committee are to provide timely peer reviews of ancillary study proposals, minimize scientific overlap, and ensure optimal utilization of ALFSG database, serum bank, and liver tissue resources. At the December 2002 meeting, the committee reviewed the status of the approved ancillary studies from the past year. Per table 1 (see page 7), multiple ancillary studies involving the etiology, prognosis, and mechanism of ALF are underway. The committee encouraged site investigators to submit a three to four page written proposal that includes study aims, background, methods, sample size calculation, data analysis plans, references, and ALFSG resource requirements. In particular, the committee encourages investigators to submit proposals regarding intracranial pressure monitoring and herbal products.

Steering Committee:

The function of the Steering Committee is to provide advice to the PI concerning issues affecting the entire study. Current members are: Anne Larson, Andy Blei, Santiago Munoz, Mike Schilsky, and Jeff Weinstein. Several issues were reviewed at the annual meeting. First, it was elected to close several sites for non-participation. Miami and Yale had been closed previously. These closures often reflect a change in personnel or simply a change in philosophy at the school involved. The committee members voted to close the University of Cincinnati adult site and USC adult site after more than a year for each without completing IRB approval.

A second issue dealt with at this meeting was enrollment in the NAC study. This is a high priority for NIH and for our DSMB. The committee approved the appointment of a recruitment committee chaired by Lorenzo Rossaro and consisting of Atif Zaman, Raj Satyanarayana, and Win Harrison. A number of suggestions were brought forward including the use of

Ancillary Study	PI	Review	Status
Gc-Globulin	Lee, UTSW	2/25/02	Manuscript in preparation
Thrombopoietin	Schioldt, UTSW	5/3/02	Manuscript in preparation
Apoptosis	Chung, MGH	2/25/02	Data being generated
TGF-B	Davern, UCSF	2/25/02	In process
Oxidative Stress	Schilsky, Mt Sinai	2/25/02	Data being generated
Histology	Hay, Mayo	2/25/02	In process
Infections	Hay, Mayo	2/25/02	Deferred
Clinical Management	Hay, Mayo	7/23/01	Ongoing data analyses
Parvovirus B-19	Brown, NIH	2/25/02	Data being generated
Hepatitis E	Dawson, Abbott labs	5/3/02	Data being generated
HBV Genotypes, Mutants	Lok-Fontana, UMich	9/1/02	Data being generated
APAP Adducts	Davern, UCSF	9/1/02	Data being generated
Long-Term Outcomes	Fontana, UMich	12/1/01	Ongoing data collection at all sites
Serum Phosphate	Davern, UCSF	2/3/03	Approved
Microarray- Viral Discovery	Ganem, UCSF	2/3/03	Under revision

Table 1 - Ancillary Studies

plastic cards with the important phone numbers for enrollment. Another idea was the use of a mailing to referring M.D.'s, with a copy of the *Annals* article and a cover letter. These will be implemented.

A final item was overall governance. It was again emphasized that the study will only be successful if all have bought in and if the committee structure works. We have had moments when the publications committee was not fully consulted regarding new manuscripts, and when the Serum Bank committee was not consulted (although the Ancillary Studies committee was) for new studies involving the serum bank. These matters were brought before the whole group at the final closing session and the Central Site will make every effort to strictly adhere to this policy.

- Will Lee spoke as an FDA-invited speaker at a meeting, on September 8th of the OTC Analgesic committee, about the ALF Study results regarding acetaminophen. The committee strongly supported improved package labeling for acetaminophen, but did not tackle the problem of package size or the use of blister packs, both in effect in the United Kingdom.
- Dr. Lee also spoke on January 28th at a symposium in Washington, D.C. on Drug-Induced Hepatotoxicity. Attendees were mainly from FDA and the pharmaceutical industry. He reviewed data from the ALF Study regarding acetaminophen and idiosyncratic drug reactions.
- The ALF Study Group has been invited to submit a Position Statement on Acute Liver Failure to the Practice Guidelines Committee of AASLD. We were initially asked to do a Practice Guideline, but few controlled studies of this condition are available. Perhaps once the NAC study and Eileen Hay's therapy study are completed, a full Practice Guideline might be possible.

ALF Landmarks

- December 17th was the day of publication of our overview paper in *Annals of Internal Medicine*. Congratulations to all who helped make this study possible.
- The ALF Study Group was featured in the "This Month from the NIH" column, written by Dr. Jay Hoofnagle, in the December issue of *Hepatology*. We were cited as a model for multi-center studies and as a rich resource for further productive studies in the future.

Housekeeping (Continued from page 3)

Lastly, we understand the timing of the meeting was not convenient for many, and thank you for taking the time out and joining us. We anticipate having the next meeting December 7th and 8th, 2003. Thank you again for all your support. We could not do it without



Grace and Annika Samuel

A Fond Farewell

Grace Samuel, pictured at left with her daughter Annika, has decided to leave us here at the Central Site. She has been working with Dr. William Lee at UT Southwestern since 1998. Grace was the Principal Study Coordinator for the Acute Liver Failure project since its inception until early last year, when she handed over her responsibilities to Ezmina Lalani. Grace worked closely with Dr. Ostapowicz, Dr. Schiødt, and Dr. Lee in writing the ALF Manual of Operations and various other documents to get this study up and running. Since the birth of Annika, she has been working part-time with Dr. Lee on various publications. All of us here at the Central Site sincerely thank Grace for all her contributions. Grace, we will miss you!

Save the Date...

February

21st: Monitoring Visit at Mayo Clinic, Jacksonville

March

13th-14th: Monitoring Visit at University of Alabama, Birmingham

27th-28th: Monitoring Visit at Northwestern University

April

3rd-4th: Monitoring Visit at University of Washington Medical Center

21st: Monitoring Visit at Mount Sinai

May

29th-30th: Monitoring Visit at Mayo Clinic, Scottsdale

Publication News

Frank Schiødt's paper on viral hepatitis in ALF has been accepted by *American Journal of Gastroenterology* and should appear in the February or March issues.

Dr. Schiødt's paper on thrombopoietin in ALF has been accepted for *Hepatology*, not certain which issue at this point.

Anne Larson has undertaken an extensive review of the ALF Study group's experience with acetaminophen toxicity. This paper was initially turned down by *New England Journal of Medicine*, but is being revised for submission there or elsewhere.

A manuscript on an acetaminophen scoring system is in draft form. The idea is to provide a uniform way of determining the likelihood that a given patient has acetaminophen toxicity. This should be particularly useful when important data points are missing.

Will Lee has been asked to do a review of the US ALF Study Group results for the August 2003 issue of *Seminars in Liver Diseases*.

Visit Us on the Web!

Take a few moments to check out our website for the Clinical Center for Liver Diseases at UT Southwestern Medical Center at Dallas. You can also view the online version of *The Target* in Adobe Acrobat® PDF format.

www3.utsouthwestern.edu/liver

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