



THE TARGET

Targeting Acute Liver Failure in the 21st Century!

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IN THIS ISSUE

Cognitive Status Following
Recovery from Acute Liver
Failure

Page 2

How the NAC Study
Works Behind the Scenes

Page 3

Pediatric NAC Study

Page 3

That Time of Year Again!

Page 4

IN EVERY ISSUE

Target Puzzler

Page 5

Publication News

Page 6

Save the Date . . .

Page 6

As of August 31st, we passed the 3/5ths point in the life of the current ALF grant period. That means that the grant expires on August 31, 2005. While it may seem a long way off, it is not! We have accomplished a lot but there is much more to do. First and foremost, we must complete the NAC study. With 75 patients currently, we are pushing up the numbers each month, but it still remains a slow process. I ask you once again, if there is anything you can do to encourage enrollment at your site, to ensure that cases are not missed, we would appreciate your undivided attention toward this study for the short period remaining.



We have surmounted a number of hurdles along the way: the issue of consent of an altered patient continues to confound us. Sites in California and New York tend to demand a specific research proxy in place signed by the patient before their illness! Our NAC supplier stopped producing the drug, but we now are fortunate to have found a new supplier without loss of continuity of the study. The biggest hurdle is that of being vigilant for new cases and continuing to bend every effort to enrolling; being ready to enlist new cases at every site, every day. We can make 200 cases in the next two years if we all pull together.

Competing Supplement

I am pleased to report that we got a very favorable review of our competing supplement request. The gist of this request was to increase funding for the expanded number of sites, now 24 as compared with 15 in the original grant application. In addition, we asked for support for the Long-Term Follow-up Study (LTFU) under Bob Fontana's direction, and for three additional small grants for pilot ancillary studies: apoptosis markers, metals as markers of oxidative stress, and APAP adducts as markers of acetaminophen damage. The review of these latter proposals was less favorable, the reviewers suggesting that we need to flesh out the requests in more detail and perhaps present as R21 pilot projects, which would, in fact, bring more money to us. We will be funded to the support of the expanded nature of the study and for the LTFU, but not for the ancillary studies. We are still enthusiastic about the ancillary studies, and will continue these studies regardless, though perhaps on a reduced scale.

We had an initial teleconference in August to roll out the added details of the psychometric testing for LTFU patients. This should not be too arduous, and comes with extra money to support this additional effort. We don't expect that it will be possible on all patients, but many should be willing to participate. The Michigan group will coordinate small teleconferences and information sessions to get this launched. We are sorry for the additional burden, but this was a strong suggestion of the NIH review team and we think a good one. Quality of life studies are not equivalent to the simple psych tests that we will now be using.

Other News

Here are some other issues we are currently working on. First, the pediatric NAC study is just under way and we look forward to hearing of its early successes. Rob Squires has enlisted help

(Continued on page 4)

Cognitive Status Following Recovery from Acute Liver Failure

by Robert Fontana, M.D.

Many patients who recover from acute liver failure (ALF) complain of impaired daily functioning including poor memory, forgetfulness, and reduced occupational performance. A recently published study of seven ALF transplant recipients demonstrated multiple deficits in cognitive function. Whether these changes are the result of critical illness, cerebral edema, or adjusting to a new health state remains unclear. To better characterize

the clinical and functional outcomes of ALF spontaneous survivors and transplant recipients, the Long-Term Follow-up study (LTFU) was designed and approved by the ALFSG steering committee in December 2001. The study, led by Dr. Robert Fontana of the University of Michigan, involves a brief clinical and medical history, blood draw, and completion of two quality of life forms by ALF patients at the one and two year follow-up visits. Over the past year, 48 LTFU study visits were completed at seven sites.

We are now pleased to inform you that the LTFU study was approved for additional funding by the NIH in June 2003. Although the scientific reviewers and NIH felt that this was an important area to study, they strongly recommended that formal neuropsychiatric testing be incorporated into the research protocol. Linas Bieliauskas, M.D. a neuropsychologist at the University of Michigan, has helped select a simple but sensitive battery of neuropsychiatric tests to administer to ALF patients at the one and two year follow-up visits. The testing which takes approximately 30 minutes to complete consists of the Trails test, as well as, the **Repeatable Battery for the Assessment of Neuro-psychological Status (RBANS)**. The Trails test is a timed exercise of "connecting the dots" that helps assess psychomotor skills. The RBANS is a brief battery of tests designed for use in research studies by non-psychiatric personnel that assesses patient performance in five domains: Immediate Memory, Delayed Memory, Visuospatial Ability, At-

tention, and Language. The RBANS test battery has previously detected subtle but clinically significant deficits in cognitive function in several patient populations. Although we will not have baseline testing for comparison amongst the ALF patients, population based normative scaling can be determined for the RBANS scores, as well as comparisons between test results at years one and two. We hypothesize that compared to population norms, ALF patients will demonstrate a degree of impaired cognitive performance at year one and have improved but persistently impaired cognitive performance at year two.

To accommodate the changes requested by the NIH, the Long-Term Follow-Up Study protocol was revised on July 1, 2003, and will be submitted to the IRB of all participating sites. While awaiting IRB approval, training materials will be sent to study coordinators for review and practice. In addition, conference calls between the University of Michigan study staff and participating centers are planned for late summer or early fall 2003, to train the study coordinators and investigators on RBANS and Trails test administration. To recognize the additional effort associated with these protocol changes, the funding for LTFU visits has been increased by 50 percent. The staff at the University of Michigan and University of Texas Southwestern look forward to working with you on this exciting project.

For further information, please call Nadia Tayeh or Robert Fontana at the University of Michigan at (734)-936-4886 or e-mail at: tayehn@umich.edu.



Above: Materials needed to administer the Trails and RBANS test at the year one and two LTFU visits.

Right: Nadia Tayeh administering the RBANS test to a healthy co-worker. RBANS is a simple but sensitive test of five domains of cognitive function that have been incorporated into the LTFU study.



How the NAC Study Works Behind the Scenes: Interaction Between the Site Coordinators, the Pharmacists, and the Study Statisticians

by Linda S. Hynan, Ph.D. and Joan S. Reisch, Ph.D.

The bi-annual Data and Safety Monitoring Board (DSMB) meeting is around the corner (October 24th) and preparations for the report are under way. The study statistician is responsible for confirming important study-related information required for the report to the DSMB.

The information provided on the NAC data forms is partially verified by the study statistician contacting the site pharmacist. In addition to determining the actual treatment randomization assignment (placebo or NAC), there are three components on this form that are confirmed by the pharmacists at a clinical site; these include patient identifiers, coma grade, and weight.

Patient Identifiers (site and patient number). To link the NAC forms with the information about the patient from the pharmacists, the research coordinator needs to provide the pharmacist with the assigned patient number that uniquely identifies the patient. Other information, such as patient initials, is not a part of the forms received for data entry and do not help in the confirmation of a randomized patient.

Coma Grade at Randomization. The coma grade (1, 2, 3, or 4) at randomization is an important feature because it helps to ensure that disease severity is “balanced” in the treatment groups. Outcome results by coma grade are provided to the DSMB committee in the report.

Weight at Randomization. The pharmacist uses weight at randomization to calculate dosing. The total dose amount is another important feature reported to the DSMB. The total amount of drug (placebo or NAC) provided to the patient based on weight are features that are compared between the two treatment groups.

Usually the calls to the pharmacist verify this information progresses smoothly. Occasionally, there is some difficulty matching essential components. Either the patient number has not been provided to the pharmacist, or the information on the form is incorrect (weight is incorrect, coma grade at admission to the study is provided rather than the coma grade at randomization, or the range of coma grade rather than exact grade is given to the pharmacist). *Patient ID, the coma grade at randomization, and weight at randomization are crucial pieces of information used in the report provided to the DSMB.* Consistency of the information between the research coordinator and the pharmacist helps make the report to the DSMB accurate.

Pediatric NAC Study by Robert Squires, M.D.

Congratulations to the following sites that have received IRB approval to begin the pediatric NAC study:

Site 10	UT Southwestern Medical Center - Norberto Rodriguez-Baez, M.D.
Site 14	Mt. Sinai Medical Center - Sukru Emre, M.D.
Site 15	University of Nebraska Medical Center - Simon Horslen, M.B., Ch.B.
Site 25	University of Alabama - Brendan McGuire, M.D.
Site 39	Kings College Hospital - Anil Dhawan, MBBS, M.D.

An additional **five sites** are well immersed in the IRB approval process, and could be approved very soon. Sample consents, NAC manual of operations and NAC protocol have been distributed to all sites to assist in the IRB application process. The procedure for adding your site to the list is as follows:

1. Notify the central site once IRB approval has been obtained
2. The central site will collect these documents: IRB approval letter and consent form, CV for PI, signed Form 1572, completed ALFSG site personnel log (Continued on page 4)

That Time of Year Again! by Julie Polson, M.D.

The start of the new academic year is upon us. The good news is that there are lots of bright new shining faces joining our various programs. Hopefully, the enthusiasm of these new recruits will infuse the rest of us with some added energy. On the other hand, with all the changes inherent in beginning a new year, things like enrolling patients in the Acute Liver Failure Study could be easily overlooked, or take lower priority. Still another concern in the summer months is that with many of us taking vacations, we may miss potential patients during periods of absence. These issues have resulted, in past years, in decreased enrollment, both in the ALF registry and in the NAC Trial, during the summer and early fall. The challenge put before the group is to use the excitement of the new year to make these next few months a period of increased, rather than decreased, enrollment. Take advantage of this time to educate new fellows and house staff about the study; make sure they are aware of how to get potential cases evaluated and enrolled. If you have not received wallet cards of study information for your site, let us know the best names and phone numbers to put on your cards, and we will get them out to you as soon as possible.

Now is also a great time to remind returning fellows, house staff and faculty about the study, and to encourage their participation in terms of expeditious referral of potential cases. Some high-impact venues for advertising the study with fliers and/or short talks include: GI and Internal Medicine educational conferences, morning report sessions, and special visits to the intensive care units and emergency departments. Please remember to designate alternate people to cover calls about potential patients if you are leaving for vacation. We can't afford to miss these cases! Once again, we must stress the importance of entering patients in the NAC Trial. NAC enrollment has been very slow these last couple months, and this issue is a major concern to the Data and Safety Monitoring Board.

A Word from the PI (Continued from page 1)

of two sites in the United Kingdom, and they are both on board early for NAC participation. Congratulations to Rob and best of luck! The pediatric protocol is slightly different, in that the period of treatment is seven days instead of three, reflecting that the pediatric patients have a more subacute disease and might benefit from this longer period of treatment.

For AASLD, we submitted six abstracts and all were accepted, including one oral and five posters. I am excited about the acetaminophen adducts study which suggests that we can tell, with a definitive blood test, when patients have sustained liver injury due to acetaminophen. This will be a valuable medico-legal test I believe and will sort out how many viral hepatitis and how many indeterminate cases are really acetaminophen toxicity or combined injury due to acetaminophen and another cause.

One Final Note

We are beginning to plan for the renewal of the grant. The submission should take place in October 2004 for a start date of September 2005. Please send us your thoughts, pro or con, concerning this. It seems obvious that this established group should keep going and stay the course. However, if you feel differently or do not intend to participate if we go forward for another five years, we need to know that now. The plan, so far, is to complete the NAC trial during the present grant period (or possibly with a short 6-12 months no-cost extension). The new grant would focus on hypothermia as a unblinded treatment for patients with all kinds of ALF. Andy Blei is taking the lead on developing the protocol for this. More news on this will follow, but be thinking of whether you wish to continue to participate. We hope you all will!

Pediatric NAC Study (Continued from page 3)

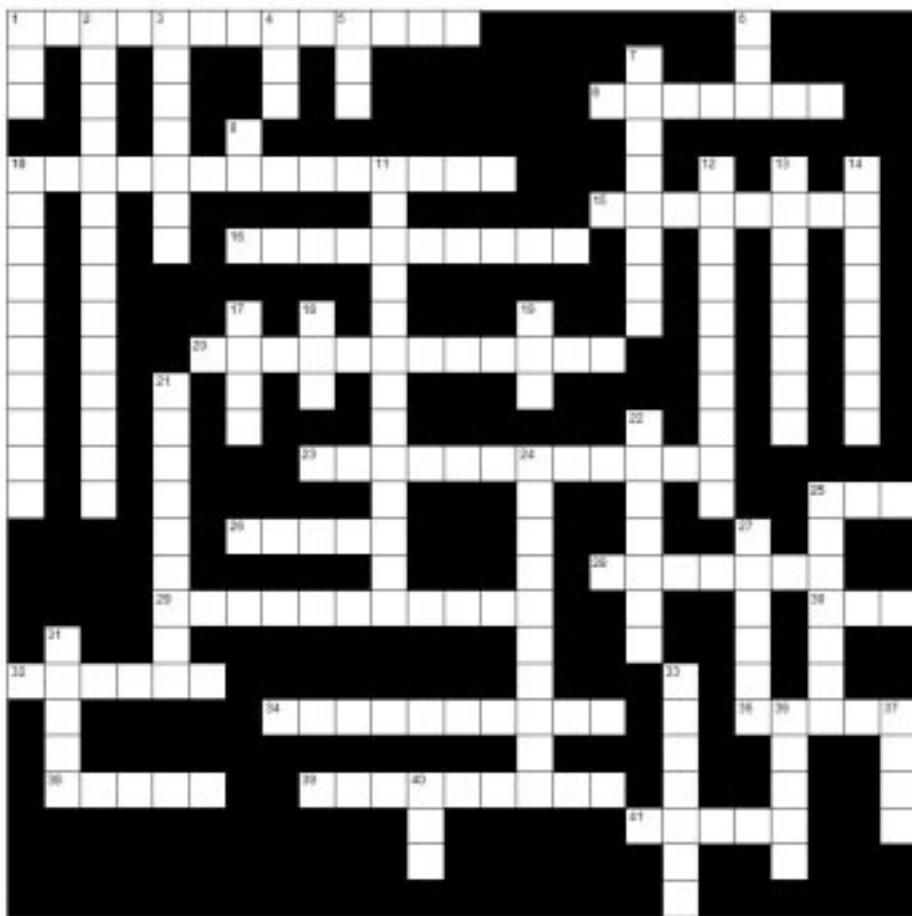
3. NAC study pharmacy forms will be sent to the Investigational Drug Pharmacist
4. NAC Randomization List will be sent to the site by Dr. Joan Reisch
5. NAC will be shipped to the Investigational Drug Pharmacist at your site

This is our opportunity to put scientific scrutiny to the question of whether NAC improves the outcome of children with non-acetaminophen ALF. Hopefully, most, if not all, of us will be able to participate in this randomized controlled trial. We need patients! The pediatric ALF registry is moving forward nicely; however we need ancillary studies, such as the NAC trial, to further our knowledge of how best to manage children with ALF.

We are awaiting the enrollment of our first patient. Let us here from you. We are available to assist you any way possible.

Target Puzzler

How about a little challenge! See if you can solve the puzzle below. Answers will appear in the next edition along with another puzzler.



ACROSS

- | | |
|---|--|
| 1. Active ingredient found in Tylenol® | 6. Principal Investigator of ALF study |
| 8. Non-active substance used in clinical trials | 7. Vitamin D binding protein is Gc _____ |
| 10. Poisonous effect on liver cells | 9. _____ Southwestern (aka Central Site) |
| 15. Yellowing of the skin | 10. The study of the liver |
| 16. Type of treatment for viral hepatitis | 11. Copper binding protein |
| 20. Test used to determine cognitive function | 12. Increase this as much as possible |
| 23. Person who analyzes incoming study data | 13. Non-cirrhotic tissue |
| 25. Type of liver enzyme (abbr.) | 14. Iron binding protein |
| 26. Extracted from blood samples | 17. Data Safety Monitoring Board (abbr) |
| 28. Doctor who will be overseeing LTFU trial | 18. Liver Cancer (abbr) |
| 29. _____ survival | 19. Study reporting form (abbr) |
| 30. NIDDK parent organization | 21. Scar tissue on the liver |
| 32. Procedure done to retrieve liver tissue | 22. Copper storage disease |
| 34. Only known human organ to do this | 24. Procedure done to replace diseased organ |
| 35. Test for encephalopathy | 25. Poisonous mushroom |
| 38. Blood filterer | 27. Study newsletter |
| 39. Viral infection of the liver | 31. If it is not bacterial, then it is _____ |
| 41. Structural protein in all mammalian cells | 33. Engorged veins in the esophagus |
| | 36. Particular test for LTFU |
| | 37. Supplementary ALF trial |
| | 40. Rare condition that can be fatal (abbr) |

DOWN

1. Another type of liver enzyme (abbr)
2. Mental changes
3. A collection of fluid in the abdomen
4. Drug used to fight acetaminophen overdose
5. Disease of the bile ducts within the liver

Publication News

Publications 2002-2003

Ostapowicz G, Fontana RJ, Schiødt FV, Larson AM, Davern TJ, Han SHB, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel GS, Reisch J, Lee WM, and the ALF Study Group. Acute Liver Failure in the United States: Results of a Prospective Multi-center Study. *Ann Intern Med*, 2002;137:947-954.

Schiødt FV, Davern TJ, Shakil AO, McGuire B, Samuel G, Lee WM, and the Acute Liver Failure Study Group. Viral Hepatitis Related Acute Liver Failure. *Am J Gastroenterol* 2003; 98:448-453.

Schiødt FV, Balko J, Schilsky M, Harrison EM, Thornton A, Lee WM, and the Acute Liver Failure Study Group. Thrombopoetin in Acute Liver Failure. *Hepatology* 2003; 37:558-561.

Vaquero J, Polson J, Chung C, Helenowski I, Schiødt FV, Reisch J, Lee WM, Blei AT and the US Acute Liver Failure Study Group. Infection and the Progression to Deep Hepatic Encephalopathy in Early Acute Liver Failure. *Gastroenterology*, 125:755-764.

Abstracts Accepted to AASLD 2003:

Chun-Tao Wai, Robert J. Fontana, Michael Schilsky, Timothy McCashland, Steven Han, Julie Polson, Munira Hussain, William M. Lee, Anna S-F Lok, and the U.S. Acute Liver Failure Study Group. Molecular epidemiology of Hepatitis B virus-related acute liver failure in the United States: a Multicenter case control study. AASLD 2003. Poster.

Davern TJ, James L, Larson A, Fontana R, Polson J, Lalani E, Hinson JA, Lee WM and the US ALF Study Group. Serum Acetaminophen Adducts Identify Patients with Severe Acetaminophen Toxicity. AASLD 2003. Poster.

Davern TJ, Polson J, Lalani E, Lee WM and the US ALF Study Group. Serum Phosphate Levels as a Predictor of Clinical Outcome in Acetaminophen-Induced Acute Liver Failure. AASLD 2003. Oral

Polson J, Ocama P, Larson AM, Hynan L, Lalani E, Harrison M, Lee WM and the US ALF Study Group. Role of acetaminophen in acute liver failure due to viral hepatitis. AASLD 2003. Poster.

Shneider B, Rinaldo P, Squires RH, Bucuvalas J, Narkewicz MR, Emre S and the Pediatric Acute Liver Failure Study Group. Prospective Analysis of Potential Fatty Acid Oxidation (FAO) Defects in Children with Acute Liver Failure using Electrospray Tandem Mass Spectrometry (ETMS) of Bile. AASLD 2003. Poster.

Squires RH, Shneider B, Sokol RJ, Narkewicz MR, Dhawan A, Jonas M, Simonds N, Hynan L, Bucuvalas J, and the Pediatric Acute Liver Failure Study Group. Autoimmune Hepatitis is an Important Cause of Acute Liver Failure in Children. AASLD 2003. Poster.

Coordinator's Corner

Remember: Blocks of tissue from transplant explants, autopsies, or liver biopsies are to be sent to UT Southwestern. Here is the address. If you have not been doing so lately, make a quick list or we can do it for you. We need more tissue!!

Coming soon: There will be some minor modifications made to the Case Report Form (CRF) that will be available near the end of the year. Be looking for them. It mostly relates to the fields around the decision to transplant on the outcome CRF.

Break out session: There will be a coordinators' breakout session on Sunday night, December 14th, after the opening dinner get-together. Be sure to be there!

Remember: Have your own study-related wallet cards? You can still request them through Chris at 214-648-9765, or fax to 214-468-3715. This may help with recruitment, and reminds the house staff about the study.

Save the Date...

October

16th-17th: Monitoring Visit at Mass General
26th: ALF Luncheon in Boston in conjunction with AASLD at the Sheraton Hotel.

November

6th: Monitoring Visit at Mayo Rochester

December

14th-15th: Annual ALF Meeting in Dallas

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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