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Richard T. James Jr. M.D.
Editor/Publisher.

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4-1 CURING CHRONIC HEPATITIS C—THE ARC OF A MEDICAL TRIUMPH: Editorial

Chronic hepatitis C is a major cause of liver cirrhosis and hepatocellular carcinoma worldwide. About 130 million to 170 million people (about 3% of the world's population, most in disadvantaged countries) are chronically infected with the hepatitis C virus (HCV). In the US, chronic hepatitis C is the most common cause of liver-related death and liver transplantation.

The development of direct-acting anti-viral agents (DAA) is revolutionalizing HCV treatment by offering genuine prospects for the first comprehensive cure of a chronic viral infection in humans.

The history of the discovery of HCV and antiviral-drug development offers a striking example of the effects of advances in biomedical research. The discovery of HCV 25 years ago showed the importance of new scientific approaches: whereas past viral discoveries had relied on direct visualization of viral particles, the previously elusive HCV was isolated with the use of a new expression-cloning approach that generated a library of complementary DNA from infected plasma.

The subsequent molecular characterization of the viral genome enabled several important discoveries:

1) It revealed HCV to be a positive-stranded RNA virus that replicates its genome directly into RNA without traversing a DNA intermediate, so that unlike HIV or hepatitis B virus, it lacks a latent, nuclear form that defies ready immunologic clearance. Instead, it requires continuous replication for its existence—an observation that would be leveraged for the design of strategies to permanently clears the virus.

2) Molecular characteristics resulted in an appreciation of viral genotypes, which led to critical epidemiological discoveries and the development of appropriate genotypic-specific therapeutic regimens.

3) It fostered the creation of several cell-culture systems to explicate the viral life-cycle, virus-host interactions, and pathogenesis.

4) Because of initial difficulty in culturing the virus, an important milestone was the construction of sub-genomic selectable replications harboring the viral non-structural proteins (NS3-5) responsible for genomic replication. The use of replications permitted efficient screening and testing of several classes of direct-acting viral agents (DAA) that blocked these proteins. These include inhibitors of NS3-4 protease, NS5A, and both nucleoside and non-nucleoside NS5B polymerase inhibitors. The subsequent discovery of a viral isolate that efficiently infected a human hepatoma cell line enabled the expansion of the arsenal of therapeutic classes to include inhibitors of viral entry, translation, and assembly, as well as inhibitors that block host proteins or microRNAs that are essential for maintenance of the viral life-cycle. Because replications and tissue-culture models largely recapitulate in vivo viral replication behavior, researchers were able to develop DAA candidates rapidly.

HCV encodes a highly error-prone RNA polymerase that generates extraordinary heterogeneity of viral species within infected persons. Thus, initial monotherapy trials of the first HCV protease inhibitors were thwarted by rapid selection of pre-existing resistant variants. A key first step in the therapeutic revolution was the addition of a protease inhibitor to the backbone of peginterferon and ribavarin. This succeeded in boosting rates of sustained virologic response, or sustained virologic cure up to 75% among patients with HCV genotype 1 infection and proved that a DAA was clinically effective. However, adverse effects limited the first-generation protease inhibitors.

The development of HCV nucleoside inhibitors, non-nucleoside inhibitors and NS5A inhibitors presented the opportunity to apply to HCV the HIV combination-therapy principle, whereby a combination of potent agents from two or more classes with non-overlapping resistance profiles could provide suppression of viral replication and prevent emergence of resistant varieties.

The FDA agreed to permit phase 2 trials to use new combinations of HCV DAAs without requiring a standard-of-care comparator. This proved catalytic. The pace of ensuing clinical drug development has been breathtaking. These trials have shown that the combination approach is capable of producing sustained virologic response rates exceeding 90% with the use of interferon-free oral combinations. Several combinations of different drug classes have all yielded high rates of sustained virolgic response in phase 2 studies. Phase 3 studies are underway with the hope that DAAs fulfill their promise in the real world. But major challenges remain.

Ultimately, a vaccine would be desirable for global eradication of HCV. But the virus's extraordinary sequence heterogeneity and the ability to evade host immune responses poses challenges for development of a broadly protective vaccine.

The introduction of DAAs represents a major breakthrough, but it is only the first step toward eliminating HCV globally.

NEJM April 24, 2014;370:1576-78 "Perspective", first author Raymond T. Chung, Harvard Medical School, Boston as.

I do not pretend to understand all of this. I do understand the message. This is a remarkable achievement, worthy of attention from the Nobel Prize Committee. Although these studies are not practical points for primary care at this time, they are so remarkable I could not resist including them.

NEJM published an astounding total of 7 studies regarding these new treatments of HCV in the April and May 2014 issues, along with 3 editorials:

1. ABT-450/r-Ombitasvir and Dasabuvir with and without Ribavirin for HCV, first author Peter Ferenci, Medical University of Vienna

2. ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis, first author Fred Poordad, University of Texas Health Science Center, San Antonio

3. Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection, first author Nezam Afdhal Beth Israel Deaconess Medical Center, Boston MA

4. Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis, first author KrinV Kowdley, Virginia Mason Medical Center, Seattle, WA

5. Treatment of HCV with ABT-450/r-Ombitasvir and Dasabuvir with Ribavirin, first author Jordan J Feld, University of Toronto Canada

6. Ledipasvir and Sofosbuvir for Previously Treated HCV C genotype 1 Infection, first author Nazam Afdhal, Beth Israel Deaconess Medical Center, Boston MA

7. Sofosbuvir and Ribavirin in HCV Genotypes 2 and 3. first author Stefan Zeuzem, Johann Wolfgang Goethe University, Frankfurt and Main, Germany

All studies reported high rates of viral response. All were industry supported.

Main adverse effects: Headache, fatigue, asthenia, nausea. Withdrawals from treatment due to adverse effects were uncommon.

Many hurdles remain. The high price will limit distribution.

4-2 MONITORING THE SAFETY OF NUTRITIONAL SUPPLEMNTS: Editorial

The CDC recently confirmed that OxyElite Pro, a popular over the counter (OTC) supplement was responsible for a cluster of cases of severe hepatitis and liver failure. The FDA, whose job it is to remove dangerous supplements from store shelves, did not learn of these cases until 4 months after the problem was suspected. By 10 months, the FDA had linked 97 cases (47 hospitalizations, 3 liver transplants, and one death) to OxyElite Pro.

It was recalled, but nothing has been done to prevent another supplement from causing organ failure or death. Nor has any change been made to improve the FDA's ability to detect dangerous supplements.

The FDA's delayed response is attributable to our woefully inadequate system for monitoring supplement safety.

Americans spend more than 32 billion dollars a year on more than 85 000 different combinations of vitamins, minerals, botanicals, amino acids, probiotics, and other supplement ingredients. Unlike prescription medications, supplements do not require pre-marketing approval. Under the Dietary Supplement Health and Education Act (1994), anything labeled as a dietary supplement is assumed to be safe until proven otherwise. The FDA is charged with the unenviable task of identifying and removing dangerous supplements only if they have caused harm.

More than 500 supplements have already been found to be adulterated with pharmaceuticals or pharmaceutical analogues, including new stimulants, novel anabolic steroids, unapproved anti-depressants, and untested sildenafil (*Viagra*) analogues. Some of the novel stimulants have never been studied in humans, and their adverse effects are entirely unknown, yet they are sold as "natural" products without undergoing any premarketing testing for safety. Some remain widely available.

Rapid detection of harms is essential to minimize risks to consumers. The FDA currently relies on MedWatch (https://www.safaetyreporting.hhs.gov) for clinicians to voluntarily report adverse events associated with prescription drugs, medical devices, or dietary supplements. MedWatch suffers from underreporting. It is less effective for detecting harms from supplements because they are sold directly to the consumer, often contain multiple active ingredients, and are too often incorrectly labeled. It may take

months or years for the FDA to gather sufficient evidence to remove the offender. Even then, the offending supplement remains in many preparations sold over the counter.

Between 2008-2010, more than 1000 supplement-related adverse events were reported to poison centers, but not reported to the FDA.

Presently, a bill is being reviewed by Congress (The Dietary Supplement Labeling ACT) that would require manufacturers to register their products with the FDA and provide safety information. But it would not improve the FDA's ability to detect and remove dangerous supplements from store shelves.

Sweeping changes would be needed to create an effective surveillance system capable of rapidly detecting supplement-related adverse effects.

With more than half of US adults taking supplements every year, at a cost of billions, consumers deserve a surveillance system capable of rapidly detecting hazardous supplements.

NEJM April 3, 2014;370:1277-80 "Perspective" by Peter A Cohen, Cambridge Health Alliance, Somerville, MA and Harvard Medical School, Boston MA

In addition, prescription drugs ordered by mail may contain unlabeled substances (including legitimately approved drugs). Some people will do anything to make a buck.

Primary care clinicians should require all patients to report every "supplement" they use and include this information on their chart.

The Dietary Supplement Health and Education Act (1994) has been a national disaster.

Under a newer law, the Dietary Supplement and Nonprescription Drug Consumer Protection Act, the manufacturer, packager, or distributor of a dietary supplement whose name appears on the label of a dietary supplement naarketed in the US is required to report to the FDA any serious adverse events received regarding the dietary supplement product when used in the US.

A brief note in BMJ May 17, 2014 The UK Medicines and Healthcare Products Regulatory Agency is warning people not to use several herbal medicines that can be bought on the internet after they were found to contain undeclared ingredients. In one case the herbal medicine Shawsa Sanijeevani, used to treat symptoms of asthma, was found to contain dexamethasone without it being declared on the label. Herbal slimming pills and a treatment for sexual dysfunction were also found to contain undeclared drugs.

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4-3 MULTI-TARGET STOOL DNA TESTING FOR COLO-RECTAL CANCER (CRC) Original Investigation

The underlying neoplastic processes of CRC lend themselves to screening. A simple, non-invasive test with high sensitivity for both CRC and advanced pre-cancerous adenomas might increase adherence rates for screening.

CRC arises from accumulated genetic alterations, which provide a basis for the analysis of stool to identify tumor-specific changes. Ongoing improvements have increased sensitivity for detection of CRC and advanced pre-cancerous lesions.

This study evaluated a multi-target stool DNA test[1] as a tool for screening, and compared it with a commercial fecal immumo-chemical test (FIT) for hemoglobin for both CRC and advanced precancerous lesions.

*(*1 *I do not understand the details of abnormalities of DNA associated with cancer. The multi-target test determines several DNA mutations associated with malignant change. It also included an immunochemical assay for human hemoglobin. Ed)*

STUDY

1. Enrolled participants (2011-12; ages 50-84) in a cross-sectional study at 90 sites throughout the US and Canada. All were asymptomatic and considered to be at average risk for CRC. Enrollment was weighted toward persons age 65 and older to increase the prevalence of cancer. No dietary or medication restrictions were required.

2. Primary outcome = ability of the DNA test to detect CRC. Secondary outcome = performance for detection of advanced pre-cancerous adenomas (polyps with high-grade dysplasia or with 25% or more villous elements measuring less than 1 cm, and sessile or hyperplasic polyps measuring 1 cm or more).

3. All received colonoscopies—the “gold standard” comparator.

RESULTS

1. A total of 12 778 participants were enrolled; 9989 could be fully evaluated.

2. A total of 65 (0.7%) were found to have CRC on colonoscopy; 60 had stage I to stage III cancers. Stool DNA test identified 60 of the 65 CRCs (sensitivity of DNA test = 92%) and 56 of 60 CRCs stage I to III (sensitivity = 93%).

3. Among 757 (7.5% of 9989) with advanced pre-cancerous adenomas, DNA detected 321 (sensitivity of DNA test = 42%). Sensitivity increased as the lesion size increased.

4. Results with colonoscopy (n = 9989)

A. Percentage of colonoscopies with CRC:

65 / 9989 = 0.65% (Most stages I to III)

B. Percentage with advanced precancerous adenoma:

757 / 9989 = 7.5%

C. Percentage completely normal;

4457 / 9989 = 45%

5. Sensitivities of multi-target stool DNA test and the Fecal Immunochemical Test: (True positives)

	Colonoscopy (n = 9989)	DNA test +	Sensitivity (%)	FIT +	Sensitivity (%)
Colon cancer					
Any	65	60	92	48	74
Stage I to III cancer*	60	56	93	44	73
Advanced adenoma (AA)	757	321	42	180	24
Non-advanced adenoma	2893	498	17	220	8

(* These stages are associated with increased rate of cure.)

6. Sensitivity of the DNA test (true positive rate) is the proportion of persons with the disease who have a positive test.

	Disease present (CRC present)
Test positive (DNA test +)	60 (true positive)
Test negative	5
Total tests	65
Sensitivity	60 / 65 = 0.92= 92%

7. Specificity of the DNA test (true negative rate) the proportion of persons without the disease (CRC) who have a negative test

Disease absent (no CRC; colonoscopy negative)

Test positive	455 (False positive)
Test negative	4002 (4457 – 455) (True negative tests)
Total tests	4457
Specificity	4002 / 4457 = 0.9 = 90% (True negative rate)

8. Comparisons with FIT:

DNA detects clinically significant lesions more efficiently than FIT

FIT resulted in fewer false positive tests.

Number of persons needed to be screened to detect one CRC: colonoscopy 154; DNA 166; FIT 208, and to detect one advanced pre-cancerous polyp: 13, 31, and 55.

DISCUSSION

1. The sensitivity of the multi-target stool DNA for detection of both CRC (92%) and advanced precancerous lesions (42%) exceeded that of FIT by an absolute difference of nearly 20 percentage points.

2. FIT was more specific than DNA for detection of both CRC and advanced precancerous lesions by absolute differences of 7 and 8 percentage points.

3. The sensitivity of DNA testing for precancerous lesions was approximately half that for detection of CRC.

5. As compared to FIT, DNA was associated with relative increase of 27% in rate for detection of stage I to III CRCs and a relative increase of 78% in rate of detection of advanced precancerous lesions.

6. Specificity is also important in cancer screening tests. It affects the number of persons who have false positive results. The specificity of FIT (95%) was superior to DNA (87%), with false positive rates of 5% vs 13%.

7. The US Preventive Services Task Force states that there is no preferable screening test, as supported by several cost-effective analyses. Offering a choice of tests may improve uptake of screening.

CONCLUSION

In asymptomatic persons at average risk for CRC, multi-target stool DNA testing detected significally more cancers than did FIT, but DNA had more false positive results.

NEJM April 3, 2014;370:1287-97 Original investigation, first author Thomas F Imperiale, Indiana University School of Medicine, Indianapolis Funded by Exact Sciences

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This article gave me an excellent opportunity to review sensitivity and specificity of a screening test. I had some difficulty since I had not thought about it for a long time. One can be easily confused. To review the well-known process:

	Disease present	Disease absent
Test positive	a	d
Test negative	b	e
Totals	c (a + b)	f (d + e)

a = number of positive tests in patients who have the disease tested for (true positive tests).

b = number of negative tests in patients who have the disease tested for (false positive test).

c = sum of positive and negative tests in patients who have the disease.

Sensitivity = a / a + b = proportion of patients <u>with</u> the disease who have a <u>positive</u> test

(true positive %).

d = number of positive tests in patients who do <u>not</u> have the disease.(false positive test).

e. number of negative tests in patients who do not have the disease (true negative).

f = sum of positive and negative tests in patients who do <u>not</u> have the disease.

Specificity = e / d + e = % of patients <u>without</u> the disease who have a <u>negative</u> test.

(true negative %)

False positive tests are the bug-a-boo of screening tests

In this study, one in ten participants had a false positive DNA test. False positive tests lead to anxiety, bother, inconvenience, additional costs of follow-up tests and interventions. This is why mammography and prostate specific antigen testing has lost appeal.

I do not know the exact process involved in a DNA screen, or the costs. DNA testing is costly.

This test is not a practical point for primary care at this time. I abstracted the article because it presented a good opportunity to review sensitivity and specificity.

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4-4 OSELTAMIVIR (*TAMIFLYU*) FOR INFLUENZA IN ADULTS AND CHILDREN: Systematic Cochrane Review of Clinical Studies Reports and Summary of Regulatory Comments

This study asks: what is the regulatory evidence from randomized controlled trials (RCTs) of effectiveness and harms of oseltanivir for treatment of influenza in all age groups?

Neuraminidase inhibitors are used globally for treatment and prevention of influenza. However, the evidence of their effectiveness in preventing complications of influenza is lacking. To address reporting bias in trials of oseltamivir, this study included only full clinical reports of RCTs and relevant regulatory comments (roughly 150 000 pages; 20 randomized trials). This is the first time that such methods have been used in a Cochrane Review.

Examined clinical study reports of RCTs testing the effectiveness of oseltamivir for prophylaxis and treatment of influenza in healthy people, or in the chronically ill, who have symptoms of influenza-like illness. These were augmented by regulator's comments and reports during drug registration.

Primary outcome = symptom relief, symptom prevention, hospitalization, complications, and harms of treatment.

Main results and the role of chance:

In trials of treatment of influenza, oseltamivir had modest symptomatic effects. It reduced the time to first alleviation of symptoms in adults by 16.7 hours. It had no effect in asthmatic children, but did benefit otherwise healthy children—time to first alleviation of symptoms = a mean of 29 hours.

There was no difference in hospitalizations in adults, and sparse data in children.

Secondary illness data (eg, pneumonia) was captured by participant self-report in 15 of 20 trials, oseltamivir reduced unverified "pneumonia" in treated adults, but the effect was not significant in the 5 trials that used more detailed diagnostic criteria for pneumonia. The effect for children was not significant, and there was no other self-reported complication of influenza.

In adults, oseltamivir increased the risk of nausea and vomiting. In children, it induced vomiting. It also increased psychiatric adverse events, headaches, and renal events. Number needed to harm = 94

In prophylactic trials, oseltamivir reduced the proportion of symptomatic influenza in individual by 55% during 42 days of follow-up.

There was a higher risk of bias for included outcomes due to missing data, selective reporting, possibly active placebo, lack of outcome definitions, suboptimal measurement, and incomplete reporting in the clinical study reports.

Summary answer to the introductory question: oseltamivir shortens the duration of influenza-like illness symptoms in adults and non-asthmatic children, and prevents their appearance in prophylaxis, but also causes nausea and vomiting and increases the risk of headaches and renal and psychiatric syndromes. Its effects on pneumonia are doubtful because of the lack of verifiable outcomes.

BMJ April 12, 2014; 348:11 BMJ2014;:g2545 doi:10.1136/bmj.g2545 Systematic Review, first author Tom Jefferson, Cochrane Acute Respiratory Infections Group, Rome, Italy

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Will a 55% reduction in spread of influenza to contacts have any benefit in reducing the likelihood of an epidemic? The authors did not comment.

Patients with influenza will have to decide whether a short reduction in duration of symptoms is worth the risk of adverse effects and the costs of these drugs vs. symptomatic treatment.

ZANAMIVIR (*Relenza*) FOR INFLUENZA IN ADULTS AND CHILDREN: Systematic Review of Clinical Study Reports BMJ April 12, 2014;348;12 BMJ2014;348:g2547, first author Carl Heneghan, University of Oxford, Oxford UK appears in this issue of BMJ.

This Cochrane Review asks the same question and relies on the same data as the preceding article and reaches similar conclusions.

Zanamivir slightly improves the time to symptomatic improvement in adults (but not in children) with influenza-like illness, although this effect is attenuated by symptom-relief medication, and has only minor harmful effects (except for bronchospasm). It did not reduce the risk of reported or confirmed pneumonia. Evidence of hospital admissions was un-assessable. These results do not support a reduction in symptoms or subsequent risk of transmission**.**

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4-5 THE TAMIFLU TRIALS: Editorial comments on the preceding articles

These Cochrane reviews of the neuraminidase inhibitors oseltamivir and zanamivir provides the most complete analysis so far of what is known from randomized trials about the effectiveness and safety of these anti-viral drugs.

It is also the culmination of a four and a half year battle for access to the raw data from industry-funded trials of oseltamivir, a drug on which the world has spent billions of dollars.

Through their exhaustive scrutiny of the data contained in clinical study reports (CSRs; the lengthy documents held by the drug's manufacturer Roche and previously seen only in part by regulators) the Cochrane authors have set exacting new standards for systematic reviews and decision makers. The fight for the data has also shown us, in more detail than ever, that the entire system of drug evaluation and regulation is deeply flawed.

In the process of the oseltamivir review, and during the long battle for access of the raw data, the Cochrane reviewers have become pioneers.

The complete evidence paints a much less positive picture of oseltamivir than was presented to regulators, policy makers, clinicians, and the public. Benefits were overestimated and the harms under-reported. In particular, the review found no compelling evidence to support claims that oseltamivir reduces the risk of complications of influenza, such as pneumonia, and hospital admissions, claims that were used to justify international stockpiling of the drug.

No trial was undertaken during a pandemic—a squandered opportunity that may come back to haunt us.

The European Medicines Agency has passed a new regulation that will require all clinical trials to be registered, all results published, and all CSRs to be made public.

BNJ April 12, 2014;348:78 BMJ2014;348:g2547 Editorial, first author Elizabeth Loder, Clinical Editor BMJ London.

None of the RCTs was independent of the manufacturer. All were against placebo rather than against standard drugs for relieving symptoms.

When reading an article about a new drug, I always try to determine the sponsor or funder. If it is a drug company, I look for "spin" and bias. Both are common.

BMJ published several additional commentaries of Tamiflu in this issue.