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A precision medicine model for targeted NSAID therapy in Alzheimer's disease

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Abstract

Background.—To date the therapeutic paradigm for Alzheimer's disease focuses on a single intervention for all patients. However, a large literature in oncology supports the therapeutic benefits of a precision medicine approach to therapy. Here we test a precision-medicine approach to Alzheimer's disease therapy.

Methods.—To determine if a baseline, blood-based proteomic companion diagnostic predicts response to NSAID therapy. Proteomic assays of plasma from a multicenter, randomized, double-blind, placebo-controlled, parallel group trial, with 1-year exposure to rofecoxib (25mg once daily), naproxen (220mg twice-daily) or placebo.

Results.—474 participants with mild-to-moderate AD were screened with 351 enrolled into the trial. Using support vector machine (SVM) analyses, 89% of the subjects randomized to either NSAID treatment arms were correctly classified using a general NSAID companion diagnostic. Drug-specific companion diagnostics yielded 98% theragnostic accuracy in the rofecoxib arm and 97% accuracy in the naproxen arm.

Conclusion.—Inflammatory-based companion diagnostics have significant potential to identify select patients with AD who have a high likelihood of responding to NSAID therapy. This work provides empirical support for a precision medicine model approach to treating AD.

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Keywords

Alzheimer's disease; precision medicine; biomarkers; proteomics; bioinformatics; clinical trial; inflammation

Introduction

Currently, over 5 million Americans suffer from Alzheimer's disease (AD; the most common form of neurodegenerative dementia)[1] and it is estimated that those numbers will grow exponentially by the year 2050. AD has an annual health care cost similar to that of cardiovascular disease and more than cancer[2]. While death rates due to cancer has declined in recent decades, death rates due to AD have steadily increased[1]. This discrepancy is, in part, due to significantly improved treatment response in cancer therapeutics offered by the precision medicine model. Here we test a novel precision medicine model for targeted NSAID therapy to specific patients suffering from AD.

While a precision medicine approach of targeting specific subpopulations of patients most likely to respond to a given therapy has been proposed for AD[3, 4], few studies have explicitly tested this paradigm. Precision medicine is, at its core, a companion diagnostic driven therapy, an approach has led to significant advancements in cancer therapeutics[5]. We have previously operationalized the concept of precision medicine for AD as "biomarker-guided therapy on a systems-level that takes into account methodological advancements and discoveries of the comprehensive pathophysiological profiles of complex multi-factorial neurodegenerative disease"[4]. The goal of this approach is to shift away from the classic "one-size-fits-all" approach towards a biomarker guided molecularly tailored therapy for AD patients[4]. In 2001, Spear and colleagues[6] estimated that efficacy rates in oncology were about 25%. Subsequently, significant improvements have been achieved through the use of companion diagnostic (CDx) driven therapy[5] following the development of trastuzumab for the treatment of specific patients with a particular biomarker positive form of breast cancer[7, 8]. For most chronic diseases, such as AD, early diagnosis and intervention are two fundamental components of therapy and companion diagnostic guided precision-medicine can significantly advance therapeutics[8]. We hypothesize that the application of a biomarker-guided approach to AD targeting specific interventions to appropriate molecular pathways will increase effectiveness of therapies as has been seen in oncology.

Profiling biological pathways associated with neurodegenerative disease has been posited to highlight novel pathways for therapeutics[9, 10], with inflammation being a major implicated pathway[11, 12]. In animal models, inflammation has been linked to AD-like pathology[13, 14] and anti-inflammatory compounds have been shown to reduce pathology and improve cognition[15–17]. In humans, inflammatory markers have been found in association with both neurofibrillary tangles[18] and senile plaques[19] in AD tissue. Multiple cohort studies support a link between inflammation and AD[20–22] with a recent meta-analysis of 175 published studies (pooled sample size >13,000) demonstrating alterations in multiple inflammatory markers (including IL6, CRP and TNFα) among AD

patients[23]. Additionally, a meta-analysis of nine published longitudinal studies (pooled sample size = 14,654) found a protective effect of NSAID use in terms of AD development with the relative risk of 0.27 (95% CI = 0.13–0.58) associated with long-term use[24]. We have consistently found inflammation alterations (including IL6, CRP and TNFα) as a key component to our serum-based proteomic profile for the detection of AD[25–28]. Based on these findings, it has been proposed that anti-inflammatory compounds have potential for treating AD and other neurodegenerative diseases[22, 24, 29–33]. However, despite many attempts, no randomized clinical trial using NSAIDs for treating or preventing AD have met predefined trial outcomes despite promising early phase clinical trial data[34–36]. Here we apply a first-of-a-kind proof of concept precision medicine approach to examine the utility of NSAIDs in the treatment of AD. We hypothesized that blood-based biomarker profile of inflammation can be used for the generation of CDx-guided NSAID therapy for specific patients suffering from AD. It is our hypothesis that the previously conducted NSAID trials were in fact successful for specific subgroups of patients. We therefore hypothesized that the trials would have been successful if appropriate inflammation-related CDx's were utilized for the identification of specific patients who were most likely to respond to NSAID therapy. The aim of the current study was to test this hypothesis in one of these trials using existing pre-randomization blood samples and data from a previously conducted clinical trial testing the efficacy of two NSAIDs (naproxen and rofecoxib) for the treatment of AD[35].

Materials and Methods

Participants were in the previously published Alzheimer's Disease Cooperative Studies (ADCS) anti-inflammatory clinical trial (P. Aisen, Project PI [35]). A full description of the sample has been published[29]. This multicenter, randomized, double-blind, placebo-controlled parallel group trial involved 1-year exposure to study medications across forty ambulatory treatment centers affiliated with the ADCS. Individuals with a diagnosis of probable AD (n=351) were recruited from December 1999 to November 2000 and randomized to one of the following treatment arms: rofecoxib (25mg once daily), naproxen (220mg twice-daily) or placebo. Inclusion criteria were as follows: age 50 or older and MMSE score of 13–26. Stable use of cholinesterase inhibitors was allowed, Exclusion criteria were: presence of comorbid conditions that increased risk for adverse events associated with NSAID treatment (hypersensitivity to aspirin or NSAIDS, active peptic ulcer disease (5yr), renal insufficiency [serum creatinine level >1.5mg/dL or >132.6umol/L], clinically significant liver disease, poorly controlled hypertension, congestive heart failure, or bleeding ulcer); comorbid conditions that might respond to NSAIDs (e.g. inflammatory arthritis); history (2mo) of regular use of inflammatory medications (aspirin at a daily dose <=325mg was allowed), neuroleptics, antidepressants, sedatives, anti-Parkinsonian medications, or any investigational treatment for AD. AD diagnosis was based on the NINCDS-ADRDA Work Group Criteria[37].

A total of 88 completed (111 randomized) the placebo arm, 90 completed (118 randomized) the naproxen arm and 89 completed (122 randomized) the rofecoxib arm. In order to determine if a proinflammatory endophenotype companion diagnostic can predict response (adverse and positive) to NSAID therapy, the analyses focused on the treatment arms similar to the approach utilized in cancer trials. Baseline plasma was available from n=123 subjects

across the NSAID treatment arms (naproxen n=68, rofecoxib n=55). Given that the hypothesis was that those with high levels of inflammation would respond positively whereas those with low levels of inflammation would experience adverse response (i.e. rapid cognitive decline), these arms were their own comparison cohort. For comparison purposes, follow-up analyses were conducted in the placebo group (n=64) to demonstrate that the NSAID drug-specific *inflammatory-based* companion diagnostics were superior in predicting treatment response. All samples were collected according to IRB approved protocols with written informed consent obtained.

Blood samples were collected and processed per the original clinical trial methods[35] with samples stored centrally at the ADCS Biomarker Core biorepository. For the current study, pre-randomization, baseline plasma samples were shipped to the first author's laboratory and assayed. Proteomic assays were conducted in duplicate via a multi-plex biomarker assay platform via electrochemiluminescence using the SECTOR Imager 2400A from Meso Scale Discovery (MSD; http://www.mesoscale.com) using published protocols[28]. All proteomics included were assayed as part of this study, not as part of the original clinical trial protocol. The selected proteins assayed included TNFα, CRP, IL6, and IL10. These specific markers were selected due to the literature linking each of them to AD[33, 38–40], including a recent meta-analysis[23]. We recently reported the analytic performance of each of these four markers for >1,300 samples across multiple cohorts and diagnoses (normal cognition, MCI, AD)[41]. When examining data from >2,000 assayed sampled, the lowest level of detection (LLOD) range (pg/mL) for TNFα, CRP, IL6, and IL10 were 0.01–0.13, 0.69–19.8, 0.01–0.11 and 0.01–0.15, respectively. The mean and standard deviation (pg/mL) for each of the markers in AD cases specifically (from >300 subjects) was as follows: TNFα = 3.4(3.2), CRP 742,972.9(3,144,226.5), IL6 7.1(63.1) and IL10 5.1(29.0)[41].

The companion diagnostics (NSAID-general and NSAID-specific) were generated using support vector machine (SVM) analyses[25–28, 42]. SVM is based on the concept of decision planes that defines decision boundaries and is primarily a classifier method that performs classification tasks by constructing hyperplanes in a multidimensional space that separates cases of different class labels. SVM analyses have the capacity of simultaneously taking into account a large volume of data to generate an overall profile (e.g. over and under-expression of select proteins) that most accurately classifies multiple outcomes rather than only binary outcomes. As with all learning machine methods, a primary concern is that of overfitting the data. In order to avoid this problem we: (1) restricted the number of proteins included in the CDx to a total of four inflammatory markers each with a substantial literature linking them with AD and cognitive decline from our previously established larger blood-based profile[28, 41]; (2) built the CDx responses in only three groups to create a CDx for clinically meaningful treatment response (i.e. stable or improvement over 12-months) to be compared to those expected to have adverse response (i.e. raid decline); (3) conducted internal fivefold cross-validation within the sample with the SVM analyses. The SVM analyses were conducted with the e1071 package (v1.6–8) in R (v3.4.2). In order to build a SVM model to predict treatment response, the radial basis function kernel were used together with five-fold cross-validation, cost=100 and gamma=0.001. The original data was randomly partitioned into 5 equal sized subsamples. A single subsample was retained as testing set and the remaining 4 subsamples were used as training set. For each model, we run

the cross-validation randomly five times. The range of cross-validation accuracy and the mean cross-validation accuracy for all the models are provided with the results.

Additionally, in order to avoid influence of outliers, common in proteomic data, all outliers beyond the fifth quintile were *set at* the fifth quintile. Finally, due to instability of assays at extremely low levels, any assay values below the standard curve were *set at* the least detectable limit for the particular assay. These approaches restricted any influence of outliers in any direction. SVM does not assume normality and, therefore, raw data were utilized. The SVM model was applied first to both treatment arms for a NSAID-general CDx and then to each arm individually for NSAID-specific CDx generation. Given overlapping and non-overlapping mechanisms of the NSAIDs, we hypothesized that drug-specific CDx's would improve prediction accuracy as is the case with other in vitro diagnostic (IVD) tests.

Results

Demographic characteristics of the cohort are in Table 1. The full characterization of the cohort can be found elsewhere[29]. Across both NSAID treatment arms, 50 (41%) participants showed a stable or improved MMSE score over the course of the 12 month trial (responder), 24 (19%) declined within measurement error (1–2 points), whereas 49 (40%) declined 3+ points on the MMSE over the 12-month period.

First, a SVM-based NSAID-general CDx was estimated to predict treatment response amongst the entire cohort (Table 2). The accuracy of this NSAID CDx in predicting treatment effect was 89% (range of five-fold cross-validation accuracy = 0.80–0.96; mean five-fold cross-validation accuracy = 0.89). The general companion diagnostic correctly identified 41 of the 49 decliners (84% accuracy), 22 of the 24 non-responders (92% accuracy), and 46 of the 50 responders (92% accuracy). See Table 2.

Next, analyses were conducted within each NSAID treatment arm to create drug-specific companion diagnostics with increased theragnostic accuracy (Table 2). The naproxen-specific companion diagnostic (Naproxen-CDx) yielded an overall accuracy of 97% in predicting response (range of five-fold cross-validation accuracy = 0.92–1.0; mean five-fold cross-validation accuracy = 0.97). It correctly identified 26 out of 26 (100% accuracy) of the rapid decliners, 10 out of 10 (100% accuracy) of the nonresponders, and 30 out of 32 (94% accuracy) of the responders. See Table 2.

The rofecoxib-specific companion (Rofecoxib-CDx) diagnostic was 98% accurate (rage of five-fold cross-validation accuracy = 0.90–1.0; mean accuracy = 0.98) in identifying treatment response (Table 2). The Rofecoxib-CDx correctly identified 23 out of 23 (100% accuracy) of the rapid decliners, 14 out of 14 (100% accuracy) of the nonresponders and 17 out of 18 (94% accuracy) of the responders. See Table 2.

As shown in Table 3, the relative importance of the inflammatory proteins in the companion diagnostics changed when comparing the NSAID-general to each drug-specific companion diagnostic.

For comparison purposes, the analyses were run among the placebo group. In this group, 33 were responders, 11 non-responders and 20 rapid decliners. Overall, the proinflammatory endophenotype was 89% accurate in predicting response (range of five-fold cross-valiation accuracy = 0.77–1.0; mean accuracy = 0.89). Interestingly, 100% of the responders were identified; however, 33% of the adverse responders were misclassified as responders. Therefore, the proinflammatory endophenotype may be useful in predicting progression in AD in general; however, it is not a viable companion diagnostic for anticholinergic medications

Discussion

These results provide direct support for the feasibility of a precision medicine approach to AD therapeutics. Companion diagnostic-driven NSAID therapy suggests that patients can be identified who are likely to experience cognitive benefit or decline. Specifically, in the ADCS NSAID trial, 41% of participants were stable or had mild improvement in MMSE scores over 12-months, approximately 20% small declines, whereas 40% experienced a notable decline in cognition over 12-months. An overall NSAID-general CDx was accurate in identifying treatment response with 87% accuracy.

When we created a Naproxen-CDx accuracy improved to 97% in identifying treatment response (responder, non-responder and rapid decliner). The Rofecoxib-CDx yielded 98% accuracy in predicting treatment response. The improved accuracy of drug-specific versus NSAID-general CDx's is expected due to the fact that these drugs have both overlapping *and non-overlapping* mechanisms of action. When the relative importance of the proteins is examined across the three sets of analyses (NSAID-CDx, Naproxen-CDx, Rofecoxib-CDx), it is evident that the weighting of the markers changed.

There is a large base of epidemiological evidence supporting the notion that anti-inflammatory compounds reduce the risk of developing AD. In a prospective, population-based cohort study of nearly 7,000 individuals 55 years of age and older, all dementia-free at base line, long-term use of NSAIDs was associated with a reduced risk of developing AD (relative risk = 0.20, CI=0.05–0.83)[21]. When analyzing data from the Cache County Study, Anthony and colleagues[22] found that use of non-aspirin NSAIDs alone reduced the risk of developing AD (Odds Ratio [OR] = 0.43, CI = 0.23–0.75) and that use of non-aspirin NSAIDs and aspirin reduced that risk even further (OR = 0.17, CI = 0.04–0.48). A meta-analysis of nine published studies (pooled sample size = 14,654) further supported the notion of a protective effect of NSAID use in terms of AD development with the relative risk of 0.27 (95% CI = 0.13–0.58) associated with long-term use[24]. More recent meta-analyses [23, 43] support the notion of altered inflammatory markers in AD cases as well as the protective effect of long-term NSAID use. For example, Wang et al found that long term use of NSAIDs reduce risk of AD (RR = 0.36, 95% CI=0.17–0.74); however, randomized trials have not supported use of NSAIDs in AD treatment[43]. While NSAIDs are not currently recommended for the prevention or treatment of AD[44], there is substantial evidence of their potential benefit and further research is warranted.

Based on a substantial literature, it has been proposed that anti-inflammatory compounds have potential for treating those suffering from AD and other neurodegenerative diseases. [22, 24, 29–33]. Three clinical trial have been completed, one on AD[29], one on MCI[45], with the third being the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) [36, 46]. These studies, based on the available literature, utilized a traditional NSAID (naproxen) as well as a COX-2 inhibitor. Naproxen was utilized for several reasons. First, several epidemiological studies (see above) suggest a protective effect of non-selective NSAIDs against neurodegeneration[47]. NSAIDs block microglial activation in vitro[48, 49] and appear to reduce accumulation of activated microglia in the AD brain[50]. On the other hand, non-selective NSAIDS are also associated with toxicity and high drop-out rates[51], which makes them difficult for studies of AD patients. Rofecoxib, a COX-2 inhibitor was selected for additional reasons. First, COX-2 may play a central role in neurodegeneration[52] via excitetoxicity (glutamate and kainic acid) pathways[52]. COX-2 expression (mRNA and protein) has also been found upregulated in human AD brains[53]. At the time, it was also thought that COX-2 inhibitors would be less toxic than non-selective NSAIDs. Despite significant basic, clinical, and epidemiological literature in support of the use of NSAIDs in AD, none of these trials successfully met targeted clinical outcomes. Additionally, the ADAPT study was prematurely discontinued due to adverse events identified with rofecoxib in other studies. On the other hand, none of those trials sought to treat specific subsets of patients where inflammation played a prominent role in cognitive loss and whom were most likely to benefit from the trial. The current results suggest that targeted treatment with NSAID medications may benefit select subsets of patients with AD.

The FDA recently released guidance for the development of companion diagnostics with therapeutic products[54]. The generation of companion diagnostics during the development of the therapeutic product can drastically impact the path to market as evidenced by crizotinib and ceritinib for treatment of non-small-cell lung cancer in patients with ALK rearrangements[55–57], which resulted in shorter path to market. The development of the CDx within the pipeline of the therapeutic development can be of tremendous value; however, the pace of biomarker development has not resulted in the FDA approval of IVDs at the anticipated pace with nearly all being for cancer therapies. The current work supports a novel precision medicine paradigm[4] for the advancement of AD therapeutics. Such an approach can be applied to multi-modal therapy as well as prevention efforts and is currently being investigated further by the current team.

There are several limitations to this study which should be considered hypothesis generating. First, the sample size per arm was small. Additional studies should be undertaken to validate the current findings. Our team is currently applying the specific CDx's developed in this study to ADAPT[36] and other trials. A second limitation is the small number of inflammatory markers examined. It is likely that additional inflammatory markers will be needed for the creation of NSAID-specific complain diagnostics for targeted treatment among patients suffering from AD and future work will examine additional proinflammatory, anti-inflammatory and other inflammatory-system mediating markers. Despite the limitations, the current findings (1) point towards the potential utility of NSAIDs for the treatment of AD among specific patients, (2) suggest that a large percentage of patients should not be taking NSAIDs due to risk for cognitive decline, and most

importantly, (3) provide proof-of-concept for a novel method for clinical trials in AD. Specifically, here we provide direct evidence for a precision medicine model for addressing AD via the creation of companion-diagnostic driven therapeutics. While retrospective analysis of previously conducted trials is an important model for supporting companion-diagnostic driven therapeutics in AD, this work must be validated in prospective clinical trials. Additionally, the development of companion-diagnostics should begin early in the drug discovery phase and pair with development through animal and human trials. In the end of codevelopment, the companion diagnostic is then approved in conjunction with the therapeutic and is available for guided therapy. As has been seen in cancer, the precision medicine approach can drastically improve patient outcomes and this model needs to be fully tested in Alzheimer's disease.

Acknowledgments/Conflicts of Interest

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Table 1:

Demographic characteristics of the sample cohort

	Naproxen (n=68)	Rofecoxib (n=55)
Age	74.0 (7.8)	73.8 (7.3)
Education	13.9(3.2)	13.9 (3.2)
Gender (% female)	48%	54%
ApoE4 positive	71%	69%

Table 2.

Treatment Response Prediction Using Proteomic Profiling Analyses

	SVM Predicted Decliner	SVM Predicted Non-Responder	SVM Predicted Responder
Total Sample (93% accurate)			
Actual Rapid Decliner	41	1	4
Actual Non-Responder	1	22	0
Actual Responder	7	1	46
Naproxen Arm (97% accurate)			
Actual Rapid Decliner	26	0	2
Actual Non-Responder	0	10	0
Actual Responder	0	0	30
Rofecoxib Arm (98% accurate)			
Actual Rapid Decliner	23	0	1
Actual Non-Responder	0	14	0
Actual Responder	0	0	17

Table 3.

Inflammatory Profile Variable Importance By NSAID

	NSAID-general	Naproxen	Rofecoxib
Marker Rank			
1	CRP	CRP	IL6
2	IL6	IL6	CRP
3	IL10	TNFα	IL10
4	TNFα	IL10	TNFα