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To: Susan A. Levine, DVM, PhD
Vice President of Technology Assessment
and Editor-in-Chief

Hayes, Inc.
157 S. Broad Street
Lansdale, PA 19446

From: David A. Johnson MD FAGC
President, American College of Gastroenterology

Date: 28 September 2007

Subject: **Request for Hayes Technology assessment of serologic testing/monitoring with immunosuppressant use azathioprine/6MP**

I am writing to you on behalf of our members of the American College of Gastroenterology- an organization of more than 10,000 clinical gastroenterologists dedicated to promoting the best care for patients with gastrointestinal diseases. We understand that the Hayes Health technology assessment involves the evaluation of scientific evidence about a particular device, therapy, procedure, diagnostic test, or preventive strategy for a potential clinical use in a specific patient population. We recognize that the process of health technology assessments uses a systematic and comprehensive methodology to strengthen and support corporate healthcare decisions and policies. We recognize that policy decisions via this technology assessment process can also provide physicians and patients with valuable information to help them weigh the benefits and risks of a treatment option. As such, we are requesting that you evaluate the evidence for immunosuppressant metabolite monitoring.

The literature is now quite clear that the current medical science supports measuring the levels of 6-TG and 6-MMP (metabolites of azathioprine and 6 mercaptopurine) for monitoring and guiding select patients with IBD as well as other specific autoimmune GI diseases such as autoimmune hepatitis. These metabolite levels are particularly helpful in dealing with patients who are not responding to standard dosing as well as in all patients that have hepatic and/or hematologic consequences associated with the use of these agents.

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I will supply some background information and literature to support that these clearly should be provided- albeit at the direction of the gastroenterologist for selected patients. At present, there are non-coverage policy decisions by some insurance companies such as Wellpoint/BCBS (in contrast to other major insurance carriers e.g. CIGNA). Patients with GI diseases and their treating physicians are being told this is "investigational". The assay has been commercially available for over 7 years and is approved for use by rheumatologists using these same drugs for the treatment of rheumatologic diseases.

Background

6-Mercaptopurine (6-MP) and its prodrug Azathiopurine (AZA) are effective for the maintenance of a steroid-free remission in Crohn's Disease (CD). (1) These drugs are members of the thiopurine class of medications and are commonly used to treat patients with CD and Ulcerative Colitis (UC) who are corticosteroid dependent in an attempt to withdraw corticosteroids and maintain patients in remission off corticosteroids. 6-MP and AZA are related immunomodulators that are perceived to act through metabolites, 6-thioguanine nucleotides (6-TGN), by mechanisms that remain unclear. (2)

Discussion

Maximizing the efficacy of Inflammatory Bowel Disease (IBD) directed therapies while minimizing their toxicity remains the principal objective in developing management strategies for IBD patients. (1) 6-MP and AZA are potent immunomodulators used to treat patients with IBD to induce and maintain remission, as steroid-sparing agents, and to limit loss of tolerance to biological agents. (3)

Research has suggested that thiopurine methyltransferase (TPMT) screening can aid in minimizing toxicity while metabolite monitoring of 6-TGN and 6-methyl-mercaptopurine (6-MMP) can be utilized to optimize therapeutic response (1).

About 30% of patients with CD fail to respond to the standard doses used in most published series. Concerns regarding both short and long term toxicity are the most common explanation for their restricted use. (3)

It has been suggested that serum 6-TGN levels of greater than $235 \text{ pmol}/8 \times 10^8$ erythrocytes may be associated with a greater response rate than in patients with lower 6-TGN levels. Some investigators have also suggested that hepatotoxicity may correlate with the elevated levels of 6-MMP. (2)

Cost-Effectiveness

Strategies applying TPMT and / or metabolite monitoring to influence treatment decisions were compared to community care (CC). The impact on toxicity minimization and improved time to initial and sustained response was evaluated. (1)

Metabolite monitoring, TPMT and TPMT + metabolite monitoring strategies as compared to CC achieved an earlier time to initial response (18.66, 18.96, and 19.10 vs. 22.41 wk, respectively) and sustained response (39.83, 42.91, and 39.8 vs. 45.36 wk, respectively). Each alternative strategy was shown to dominate CC (i.e., less costs and faster time to response or sustained response). (1)

An additional issue for cost analysis should be the recognition that these assays allow for the maximal dosing to provide the target optimal benefit. Recognizably, if patients do not adequately respond to these immunosuppressants, transition to the next line of therapy with anti-TNF medications enters into a logarithmic escalation of price. This transition would be potentially unnecessary if the clinician could better direct the dosing of 6MP or azathioprine through the use of the metabolite assays.

Data Criteria

A recent meta-analysis identified 55 studies, 12 of which contained data sufficient for inclusion. Assays for 6-TGN levels were performed in a uniform fashion in 10 of the 12 studies via a modification of the high-performance liquid chromatography assay developed initially by Lennard and Singleton; in 5 of these studies the assays were performed at Prometheus Laboratories in San Diego, CA. (3)

The study by Lowry, et al used the Erdmann method, which required a conversion factor of 1.6 to convert Erdmann assay results into Leonard assay results. It is interesting to note that this study was 1 of the 2 studies using a different assay for 6-TGN levels. (3)

Data Analysis

Meta-analysis of retrospective and cross sectional studies suggests a strong association between 6-TGN levels and induction of remission among patients with IBD. This study provides strong evidence that 6-TGN levels are associated with clinical response in IBD patients taking 6-MP or AZA and thus may be useful in the management of these patients, particularly those with disease refractory to their current dose of AZA or 6-MP.(3)

Results of a pooled analysis showed that IBD patients in remission had significantly higher 6-TGN levels than those with active disease with a pooled difference of 66 pmol/8x10⁸ RBCs. It was also found that patients with 6-TGN levels above threshold values of 230-260 pmol/8x10⁸ RBCs were significantly more likely to be in clinical remission with an odds ratio of 3.27 (3)

6-TGN levels do seem to be associated with clinical remission, with higher levels observed in patients with inactive disease. Threshold 6-TGN levels of 230-260 pmol/8x10⁸ RBCs may serve as useful therapeutic targets, especially in patients with active disease. (3)

Another potential value of 6-TGN testing concerns timing of the testing. If testing is performed relatively early in the treatment course and a patient is identified as a non-

responder, exposure to therapy could be minimized, thus potentially decreasing the risk for adverse events. (3)

Thiopurine metabolite monitoring in the treatment of patients with 6-MP or AZA is useful when attempting to determine medical noncompliance and may be helpful for optimizing dose and monitoring for toxicity. (2)

Six studies reported sufficient data on threshold values of 6-TGN level to allow calculation of both the proportion of patients above and below the threshold values who were in remission and odds ratio of remission based on each threshold value. Threshold values ranged from 230 to 260 pmol/ 8×10^8 RBCs.(3)

The fact that studies with different designs, sample sizes, and patient populations reached the same conclusions could be viewed as confirmation of the associations between 6-TGN levels a disease activity in IBD patients taking 6-MP or AZA. (3)

6-TGN levels do seem to be associated with clinical remission, with higher levels observed in patients with inactive disease. Threshold 6-TGN levels of 230-260 pmol/ 8×10^8 RBCs may serve as useful therapeutic targets, especially in patients with active disease. (3)

FDA recommendations (per product instructions)

Complete Blood Count (CBC) Monitoring: Patients on azathioprine should have complete blood counts, including platelet counts, weekly during the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage alterations or other therapy changes are necessary.

TPMT Testing: It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are TPMT*2, TPMT*3A and TPMT*3C. Patients with two non-functional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable

Recommendations:

1. Current FDA recommendations suggest that individuals should have TPMT genotype or phenotype assessed before initiation of therapy with AZA or 6-MP in an effort to detect individuals who have low enzyme activity (or who are homozygous deficient in TPMT) in an effort to avoid AZA or 6-MP therapy in these patients and thus avoid potential adverse events. This may also be of particular importance in patients where

starting with a full dose rather than progressive lower starting dose escalation may be necessary due to severity of disease. This may also be of particular importance to other selected populations (e.g. pediatrics).

2. Thiopurine metabolite monitoring in the treatment of patients with 6-MP or AZA is useful when attempting to determine medical noncompliance and may be helpful for optimizing dose and monitoring for toxicity.

Potential implications of non-approval

1. Inadequate disease management with suboptimal control of disease has obvious health costs related to hospitalizations, surgery.

2. Development of potentially avoidable complications of AZA or 6 MP related hematologic complications.

3. Premature discontinuance of AZA or 6 MP with change in therapy to anti TNF options (major cost issue).

As a national society of clinicians, we recognize that the goals of the Health technology assessments are to improve the quality of care and health outcomes via establishment of medical policies and best practice guidelines. Accordingly, we are asking at this time, for an evaluation to provide a guide for managed care company coverage policy decisions to allow for genotype/phenotype testing as well as the thiopurine metabolite monitoring. This will not oblige physicians to use this testing in every case, but would allow them to incorporate testing when it is felt that this information is necessary to optimize the safety and efficacy of the treatment provided to patients with ulcerative colitis, Crohn's disease, and other autoimmune GI disease (e.g. autoimmune hepatitis) .

We believe that the published and clinical evidence around the use of these genetic and metabolite tests is strongly supportive of the use in select patient groups. Accordingly, a favorable Haynes Technology assessment would provide health care providers and their patients with the most appropriate means to cost-effectively optimize clinical outcomes for appropriate GI diseases.

References

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2. American Gastroenterological Association Institute. Medical Position Statement on Corticosteroids Immunomodulators and Infliximab in Inflammatory Bowel Disease Treated with Azathioprine or 6-Mercaptopurine. *Gastroenterology* 2006;130:935-939

3. Osterman M, Kundu R, Lichtenstien G, et al. Association of 6-Thioguanine Nucleotide Levels and Inflammatory Bowel Disease Activity: A Meta-Analysis. *Gastroenterology* 2006;130:1047-1053