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Oral budesonide is an effective alternative to prednisone for treatment of autoimmune hepatitis

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Oral budesonide is an effective alternative to prednisone for treatment of autoimmune hepatitis

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ABSTRACT A clinical decision report using:

Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology*. 2010;139(4):1198-1206. https://doi.org/10.1053/j.gastro.2010.06.046

for a patient with autoimmune hepatitis developing septic arthritis secondary to prednisone therapy.

Keywords: *budesonide, prednisone, autoimmune hepatitis, steroids*

Clinical-Social Context

Ms. Diana Walker [pseudonym], a 32-year-old woman with a past medical history of autoimmune hepatitis (AIH), fibromyalgia, and borderline personality disorder was brought to the Emergency Department (ED) with the chief complaint of right knee pain and swelling of 1-week duration. On arrival, Ms. Walker stated, "I'm in so much pain, I've tried everything I could think of, but nothing helps." A week prior to admission, she suffered a fall in her bathroom and landed on her right knee. She was initially able to tolerate the pain from the injury, but two days prior to admission her pain became more severe with the knee swollen and tender to the touch, unrelieved by home pain medications. The physical exam was significant for right knee edema and warmth, with active and passive range of motion limited by pain. Labs showed elevated ESR (94) and CRP (17.2), indicating an inflammatory process. An X-ray of the right knee showed no abnormalities, and Ms. Walker was given 2 mg of morphine for pain. The medicine team admitted Ms. Walker to the inpatient floor for further evaluation and treatment.

Ms. Walker took prednisone and azathioprine for AIH, gabapentin for fibromyalgia, and received no psychiatric care for the 3 years prior to admission. She lived with her wife and 3-year-old son, had strong ties within her community, had a stable income with excellent healthcare coverage, and had no food insecurities. Ms. Walker also took good care of her health, was compliant with her medications, had few hospitalizations, and regularly visited her primary care physician (PCP). Although she struggled with intermittent pain and mood episodes, she felt that she was able to keep her symptoms under control and received ample support from her friends and family throughout her hardships. However, the hospital setting made her feel fearful and anxious. She wanted answers about what was wrong with her and became increasingly frustrated as more tests were ordered.

Arthrocentesis of the knee was performed with results consistent with *E. coli* septic arthritis, likely secondary to immunosuppression from prednisone use for 3-month duration (initial dose 60 mg, tapered to 25 mg). Ms. Walker was given ceftriaxone for the infection and underwent right knee arthroscopic irrigation and debridement. The

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gastroenterologist recommended tapering the prednisone by 5 mg each day and replacing it with budesonide, a corticosteroid that acts locally on the gastrointestinal system. Ms. Walker had numerous concerns about this new drug. She wondered whether it would adequately control her AIH and if it would continue to put her at risk of developing complications, such as septic arthritis. She also wondered if the drug would affect her mental status. The gastroenterologist reassured her that budesonide has a lesser side effect profile and would be just as effective as prednisone. Ms. Walker was still wary of changing her medicine and wanted some time to think.

Clinical Question

Is budesonide a safer, more effective alternative to prednisone in the treatment of autoimmune hepatitis?

Research Article

Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology*. 2010;139(4):1198-1206. https://doi.org/10.1053/j.gastro.2010.06.046 [1]

Description of Related Literature

The PubMed database was searched using the query “hepatitis, autoimmune” AND “budesonide,” yielding 90 items that fit the search criteria. When filtering the population of study to adults ages 19 and older and the language to English, 24 articles remained. Articles were excluded if they did not directly compare outcomes in patients treated with oral budesonide versus predniso(lo)ne +/- azathioprine, which is the mainstay of therapy for AIH.[2] Studies were chosen which compared the capacity of these drugs to cause steroid-related side effects such as hirsutism, myopathies, weight gain, acne, and psychiatric disturbances.[3] Furthermore, studies were found that assessed the efficacy of the drugs in achieving remission of AIH, with remission commonly defined as a reduction in aminotransferase levels to less than twice the upper limit of the normal levels.[2]

Several studies showed that budesonide has potential as an effective alternative to prednisone in AIH. A chart review by Zandieh et al. showed that the majority of patients who switched from prednisone to budesonide achieved complete remission with budesonide with no reports of adverse events.[4] A cohort study by Binicier and Günay had similar outcomes in patients treated with azathioprine in combination with budesonide or prednisone. Both drug regimens showed similar rates of AIH remission with a greater rate of steroid-induced side effects among the patients treated with prednisone.[5] These studies were excluded from the critical appraisal due to their retrospective designs and small sample sizes.

Similarly, Peiseler et al. conducted a cohort study that showed that patients who switched from prednisolone therapy to budesonide had fewer side effects than patients on prednisolone, with several patients reporting an improvement in their bone density scans.[6] Van den Brand’s cohort study also assessed side effects of prednisone and budesonide and showed that increased dosages of either of the medications leads to an increased risk of side effects, such as bone fractures and cataracts.[7] However, the study noted that these adverse effects are lessened in patients treated with budesonide, suggesting that its overall side effect profile is more favorable for most patients.[7] While both studies showed that budesonide has fewer side effects, Peiseler et al’s study did not draw the same conclusion about its efficacy. The patients who initially did not respond to prednisolone therapy also did not respond to budesonide, suggesting that budesonide does not have an advantage in treating AIH in individuals who are unable to achieve remission on the standard treatment.[6] Both of these studies have their utility, but have limitations due to their retrospective design and therefore were not chosen for critical appraisal.

Importantly, another open-label pilot study conducted by Czaja and Lindor points to possible concerns when budesonide is used for the treatment of AIH. The study included 10 patients with treatment-dependent AIH and weaned them from their previous therapies to a regimen of budesonide 3 mg thrice daily. The study showed that budesonide therapy was associated with lower rates of remission, prominent steroid-related side effects and symptoms of withdrawal, and a high rate of treatment failure.[8] In contrast, the study conducted by Csepregi et al., wherein 18 patients with AIH were treated with the same dosage of budesonide, showed high rates of remission. Notably, patients who experienced steroid-related side effects were also given azathioprine and patients who had concomitant cholestasis were treated with the addition of ursodeoxycholic acid. This study found that 33% of participants

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experienced steroid-related side effects and 83% achieved complete remission of AIH.[9] Most of the treatment failures and side effects were observed in patients with a cirrhotic liver, while remission was achieved even in patients with comorbidities such as primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC).[9] Wiegand et al.'s study also produces similar results, demonstrating that a small cohort of treatment naïve patients was able to achieve remission on budesonide as a single agent treatment for AIH.[10] These studies were excluded from critical appraisal as they investigated only a small cohort of patients with AIH and did not include a comparison group with standard therapy (i.e., prednisone +/- azathioprine) as the control.

Another concern with budesonide is whether it is safe to use in patients with cirrhosis. According to several studies that assess the metabolism of budesonide, the drug is not safe for patients with cirrhosis since it is primarily metabolized by the liver. Cirrhosis causes fibrosis of the liver, impairing its ability to metabolize the drug. This results in higher levels of budesonide and its metabolites in the blood, leading to increased risk of developing steroid-related side effects in these patients.[11,12,13]

Lastly, the study conducted by Manns et al. was chosen for critical appraisal in the context of Ms. Walker. To date, this is the only randomized controlled study that directly compared the efficacy and safety of budesonide to prednisone in the treatment of noncirrhotic AIH.[1] Due to the excellent prospective design of this study, randomization, controls, and large sample size of over 200 participants, this study meets criteria for a SORT level 1 study.[14] The utility of the Manns et al. clinical trial was further emphasized in Terazoli et al.'s meta-analysis. They used the study results to conclude that budesonide has potential therapeutic value as a second-line drug, especially in patients like Ms. Walker, who have already achieved remission on prednisone but are experiencing steroid-related side effects.[15]

Overall, using the SORT criteria, the studies have a Strength of Recommendation of B due to inconsistencies regarding the efficacy of budesonide in inducing remission of AIH.[14] There is, however, strong evidence that budesonide does have a favorable side-effect profile and is a viable alternative to prednisone in a specific subset of patients, that may include Ms. Walker.

To ensure that the search is thorough and reproducible, the search was replicated through PubMed with the terms "hepatitis, autoimmune" AND "therapy." This search returned 1,908 results and was further filtered to include only adult study participants (ages 19 and older) and English as the language, yielding 903 results. Due to the large number of studies found, the results were filtered to include only clinical trials, meta-analyses, randomized controlled studies, reviews, and systematic reviews, narrowing the search to 124 articles. While this search is broader and encompasses more studies comparing various therapies for autoimmune hepatitis, it does include most of the articles found in the original search, including the study by Manns et al., and thereby confirms that the search is adequate.

Critical Appraisal

The double-blind, randomized, controlled study conducted by Manns et al. has numerous strengths, with many of them attributed to the study design. The inclusion criteria for the study were that patients had to be 10-70 years of age with acute AIH based on liver biopsy or histology findings, elevated aminotransferase levels, and elevated immunoglobulins. The diagnosis had to occur within a recent pre-defined period ranging from 0-12 months, in the absence of cirrhosis and other liver abnormalities such as hepatitis, PBC, or PSC. Importantly, only 77.5% of patients in the budesonide group and 80% of patients in the prednisone group met criteria for having a definite diagnosis of AIH, as defined by a score >15 on the International Autoimmune Hepatitis Group (IAIHG) scoring system. A probable diagnosis of AIH, with a score of 10-15 based on the IAIHG scoring system, was achieved by 20.6% of participants in the budesonide group and 18.1% of participants in the prednisone group. This illustrates that not all participants were confirmed to have autoimmune hepatitis and some participants may have had alternative diagnoses, which affects the response rates of the study.

Based on the inclusion criteria, Ms. Walker would have been an excellent candidate for this study, as she was diagnosed with acute AIH by liver biopsy 3 months before her hospital visit and had a non-cirrhotic liver and no other co-existing liver diseases. Originally, 307 participants were screened, 99 did not meet inclusion criteria and another 32 participants did not complete the study. All participants were treated equally and gave informed consent. There was also adequate double blinding, with no ability for patients to guess their treatment group. The results of the trial were not reported prior to the study's completion. Notably, most of the study's authors had conflicts of interests. The study was sponsored by Dr. Falk Pharma and many of the authors received funding

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from this sponsor in the form of lecture and/or consulting fees. Authors also received funding from other pharmaceutical companies: GSK, Novartis, Abbot, Essex, Roche, and Boehringer Ingelheim.

The 207 patients who met the inclusion criteria were randomized and separated into either a control group with prednisone or an experimental group with budesonide. For the first 6 months, patients were treated with azathioprine 1-2 mg/kg/d in combination with 3 mg of budesonide 2-3 times daily or 40 mg/d of prednisone tapered to 10 mg/d. The researchers used intention-to-treat and per-protocol analysis to measure rates of remission as well as to evaluate patients for steroid-related side-effects. The patients on budesonide reported significantly fewer steroid-related side effects and had significantly higher rates of remission. While other side effects were more prominent in the prednisone group, the rate of mood-related side effects was slightly higher (9.8% / 7.6%), but this difference was not statistically significant. Using the ITT analysis, 60/100 (60%) in the budesonide group vs. 40/103 (38.8%) in the prednisone group achieved complete remission after 6 months of therapy, with an NNT of 4.71. The second phase was unblinded and both groups received budesonide for an additional 6 months. When patients originally treated with prednisone were switched to the budesonide regimen, this resulted in a 40% decrease in steroid-related side effects. Furthermore, at the end of the second phase, there were no significant differences in the rates of treatment response between the individuals who initially received prednisone compared to those that received budesonide. Both groups had equally successful results, with 54.8% of study participants achieving complete remission at the end of the 12-month trial period.

While no information is provided regarding how the researchers obtained their study participants, they were recruited in a consecutive manner over several years. They were randomized by age, serology, and BMI. However, there were slight variations between the treatment groups in terms of gender, with a significantly greater proportion of females (84.8%) in the prednisone group compared to the budesonide group (69.6%). Importantly, the study was conducted in Europe and lacked ethnic diversity with almost 100% Caucasian participants. It would have been valuable to include ethnically diverse populations to evaluate whether similar results can be replicated, such as with African Americans in the case of Ms. Walker. Overall, the study was well-randomized, and these limitations still allow for the generalizability of the results to her case.

A major strength that sets this study apart from others is that the researchers had a more rigid definition for remission, defining it as normalization of aminotransferase levels. However, while this definition has its appeals, it also presents the dilemma that when the definition of remission is loosened, it eliminates the statistically significant differences in remission between the prednisone and budesonide groups, demonstrating that both treatment regiments are successful when looking only at reductions in aminotransferase levels. The more stringent definition reveals that a more significant remission was observed in the budesonide group, and this may have implications for better liver function and therefore better quality of life. This definition would appeal to patients like Ms. Walker, who wish to achieve a normally functioning liver and avoid being reliant on large doses of steroids for prolonged periods of time.

Clinical Application

The medical team used Mann et al's study to answer Ms. Walker's worries regarding the efficacy and safety of budesonide in treating her autoimmune hepatitis. While combination therapy of prednisone and azathioprine is considered the gold standard of treatment, the study shows that budesonide has a high likelihood of allowing noncirrhotic patients, like Ms. Walker, to achieve and maintain remission with a reduced risk of steroid-induced side effects. Additionally, since she was previously able to achieve remission on prednisone, this shows that she is responsive to steroid therapy and further increases her chances for success. The risks of the medication were communicated to Ms. Walker. She was made aware that the therapy may fail or result in steroid-induced side effects, especially given that there was a slightly increased incidence of mood-related side effects among the budesonide group and her pre-existing psychiatric condition may increase the chances of this effect.

Ms. Walker spoke to her wife and together they weighed the risks and benefits of the therapy. They decided to try the combination of budesonide with azathioprine because of the high probability of success in her case and she was asked to inform her physician if she experienced any side effects, particularly any new psychiatric symptoms or increased muscle pain. They agreed that if new side effects were observed or if there was any worsening in her liver function, the therapy would be re-evaluated, and other therapeutic options would be explored. The team also spoke with the family about the importance of providing her with support in ambulating, as her knee will be

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painful for several weeks. Ms. Walker's wife provided reassurance that they would take good care of her, they both thanked the medical team, and Ms. Walker was discharged in stable condition. She will follow-up with her primary care physician in one week for continued care.

New Knowledge Related to Clinical Decision Science

Ms. Walker's case provided the team with an opportunity to learn about an uncommon therapeutic option for AIH. We used the largest available clinical trial in constructing the patient's treatment plan. Most important, the clinical trial we used was able to address the specific concerns of our patient. This demonstrates that even with very limited clinical data, the results of a well-designed clinical trial can be extrapolated to the cases of individual patients. From this case, the takeaway is that all patients with noncirrhotic autoimmune hepatitis, without other co-existing liver diseases, can be started on budesonide. However, it is important for these patients to also have substantial resources, such as the ability to attend follow-up visits, have adequate healthcare coverage, access to transportation, and a strong support system to help manage the challenges associated with prolonged immunosuppressive therapy. Ms. Walker is lucky in this regard, but other patients may not have access to the care that they need, and this would greatly limit their opportunities to try therapies that are less tested, such as taking budesonide in the setting of AIH. While more research on this topic is needed, there is enough clinical data to make well-informed treatment decisions that will benefit Ms. Walker and future patients to come.

Conflict Of Interest Statement

The author declares no conflict of interest.

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