Rate and Predictors of Endoscopic Mucosal Healing in Biologic Naive Patients with Inflammatory Bowel Disease by Azathioprine Treatment: A Real World, 10 Years’ Experience from a Single Centre in Turkey

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Abstract

Background—There is increasing evidence that endoscopic mucosal healing (EMH) is a key target in inflammatory bowel disease (IBD) therapy. However, there is limited evidence of EMH rates with conventional IBD therapy outside of Western population groups.

Aim—To evaluate the role of azathioprine (AZA) in inducing EMH in IBD patients.

Methods—Patients with inflammatory bowel disease were evaluated in terms of endoscopic mucosal healing and the incidence of surgical interventions during the azathioprine treatment between 1995 to 2014.

Results—A total of 120 inflammatory bowel disease patients were enrolled. Endoscopic mucosal healing was found in 37% patients with inflammatory bowel disease (42% in chronic ulcerative colitis and 33% in Crohn’s disease). Male gender had a negative impact on the efficacy of
azathioprine (P<0.05). Responder inflammatory bowel disease patients were older (age at the IBD diagnose) than the nonresponder (P<0.05). Azathioprine therapy reduced the number of the surgical interventions (P<0.05).

**Conclusion**—We showed that azathioprine therapy significantly induced endoscopic mucosal healing in biologic naïve patients with active inflammatory bowel disease as well as decreasing the surgical interventions, with negative predictive factors identified by a younger age at IBD presentation and male gender.

**Keywords**
Crohn’s disease; Thiopurines; Azathioprine treatment; Endoscopic mucosal healing; Inflammatory bowel disease

**Introduction**

Inflammatory bowel disease (IBD) including Ulcerative Colitis (UC) and Crohn’s Disease (CD) are chronic, progressive and relapsing disorders [1]. Both UC and CD are characterized by inflammation and ulceration with genetic and environmental factors that contribute to disease pathogenesis.

Endoscopic mucosal healing (EMH) is now taken as a key treatment-goal in IBD management; achieving a positive modification in the natural history of IBD, and better outcomes with regard to steroid-free remission, surgery and hospitalization [2–5]. Current medical strategies for moderate to severe IBD include the use of corticosteroids, immunosuppressants (such as Azathioprine (AZA) and 6-Mercaptopurine) and biologic therapies. Newer biologic therapies (such as anti-TNF-α agents) have produced significant treatment gains in IBD, but safety and in particular economic considerations have raised concerns about its long term utilization in patients.

EMH can be achieved with both AZA and biologics, but with reported efficacy rates that differ among published studies for each agent, and that are based primarily upon White-Western populations. The incidence and prevalence of IBD is rising across Asia, but there is limited data on EMH responses across these countries, with most published studies based in East and South East Asia [6,7].

Turkey is a unique country that borders both Europe and Asia, with over 90% of its land mass in Asia. IBD incidence rates in Turkey resemble that seen in the Middle East, with no published studies of EMH rates in the region [8]. Assessing EMH responses in this population is therefore an important addition to our understanding of available treatment efficacy in moderate to severe Asian IBD patients. As such, our study aims were to evaluate the role of Azathioprine (AZA) in inducing EMH in biologic naïve IBD patients in our centre in Turkey, looking additionally for predictive factors of a positive mucosal healing response under AZA.
Significance of this Study

What is already known about this subject

The current medical management of moderate-severe IBD consists of corticosteroids and immunosuppressants.

New therapeutic approaches (such as anti-TNFα antibodies) led to a reduction in the mortality rate and a favorable modification in the natural history of patients with CD.

Safety and especially economic issues have increasingly raised concerns about the long term use of biologics as a maintenance therapy in patients with IBD.

What are the new findings

We evaluated the role of azathioprine for inducing endoscopic mucosal healing on patients with inflammatory bowel disease and to characterize factors predicting endoscopic mucosal healing by the azathioprine therapy in this study, beside the incidence of surgical interventions during the azathioprine treatment at a single tertiary gastroenterology between 1995–2014.

We showed that azathioprine therapy significantly induced endoscopic mucosal healing in azathioprine native patients with active inflammatory bowel disease through decreasing the frequency of the surgical interventions.

Male gender and young age at diagnosis were negative predictors of the response.

We showed that azathioprine therapy significantly induced endoscopic mucosal healing in biologic naïve patients with active inflammatory bowel disease as well as decreasing the surgical interventions.

How might it impact on clinical practice in the foreseeable future?

Azathioprine by a low cost will decrease the health budget in IBD. In particular, we must use more expensive biologics in selected patients or patients without response to azathioprine.

Mucosal healing should be a treatment goal because it may change the natural course of IBD.

Mucosal healing may be associated with better long-term outcomes and reduced risk of surgery.

Materials and Methods

Study design and patient characteristics

This was a retrospective study, with a total of 2700 patients with IBD identified between 1995 to 2014 at our single-center. The study was approved by the ethics committee, and data was collected on patients treated with AZA from Inflammatory Bowel Disease clinics. Eligible patients were at least 18 years of age, and had established IBD for at least 3 months; with a Crohn’s Disease Activity Index (CDAI) score of 220 to 450 points, and severely
active UC as defined according to the total Mayo score [5]. Patients were excluded if they had started AZA at another hospital, or if AZA was used primarily for another disease indication. Additionally, patients with the short bowel syndrome, an ostomy, a symptomatic, recent abdominal surgery (within 6 months), a history of Tuberculosis (or other granulomatous infections), a positive chest radiograph or tuberculin skin test were also excluded.

Therefore, in total 120 patients with IBD were included in the study; 75 patients with CD, and 45 with UC. Patients had regular clinical follow-up and endoscopic examinations at our clinic, and the efficacy of AZA treatment was only assessed if treatment had been continued for at least 4 months. EMH was defined by a full lower GI endoscopy showing no inflammation, mucus, granularity, ulceration or vascular invisibility in the rectum, colon and distal ileum. Patients were considered missed to follow up if information was lacking on clinical or endoscopic evaluation during AZA therapy. Disease extent and treatment response was defined by endoscopic and histological evidence. Efficacy data was based on the findings from the last evaluation.

Dose of azathioprine
AZA dose was increased to the nearest approximation of 2.5 mg per kilogram per day with 50 mg tablets (125 to 250 mg per day). Systemic corticosteroids was initiated (for patients not receiving them at baseline) with the dose until week 4 (maximum allowed dose, 40 mg per day). After 4th week, the dose was tapered and stopped until week 12. The continued use of oral 5-aminosalicylic acid (5-ASA) compounds was allowed.

Evaluation of efficacy and safety
Ileocolonoscopy was performed at baseline and again at week 16 or later in each patient who had mucosal active disease at the baseline examination. Each colonoscopy was interpreted by one of the experienced endoscopists for IBD patients, who were unaware of the study and the timing of the procedure. Corticosteroid-free clinical remission was defined in patients who had not received systemic corticosteroids for at least 4 wk. EMH was defined as the absence of ulceration and active inflammation by visual assessment or endoscopy score of 0–1 at week 16 in patients.

Primary and secondary end points
The primary efficacy end point was the rate of corticosteroid-free EMH at least at week 16. Secondary end point was effectiveness of AZA on surgical interventions of patients with IBD.

Statistical analyses
The data was coded and recorded in a computer using an IBM Statistical Package for the Social Sciences (SPSS; Armonk, NY, United States) for the Windows version 17.0 (2007). The Chi-square and Fisher’s exact tests were used for comparing the responder and non-responder groups for the distribution of the disease (UC and CD), gender, IBD related surgery percent prior to AZA therapy and during the AZA therapy (intestinal resection), efficacy of AZA in previously not-operated and operated patients with CD, and smoking
habit. Age at the IBD diagnosis and duration of AZA therapy were compared by Student’s t test between responder and non-responder groups because of parametric variables. Duration prior to the AZA therapy was compared by Mann–Whitney U test due to non-parametric variables. P<0.05 was considered statistically significant in all the tests.

Results

Patient demographics

Overall, 2700 patients with IBD were seen in our specialty clinic at the Türkiye Yüksek İhtisas Hospital, Ankara from 1995 to 2014; 702 patients with CD, and 1,998 with UC. A total of 120 patients treated with AZA fulfilled inclusion and exclusion criteria and were included in the study. Of the 120 patients with IBD, there were 45 (37.5%) patients with UC and 75 (62.5%) with CD, as shown in Table 1.

The mean age at IBD diagnosis was 36.9 ± 12.3 years (median: 36.5, range: 11–72) with a male to female ratio of 2:1. The mean period between IBD diagnosis and commencing AZA was 39.8 months (median: 24 months, range: 4–264). Mean duration of AZA therapy (months) was 31.5 ± 24.7 months (median: 25.5, range 4–113) in IBD patients, with a duration of 31.2 ± 25.7 (median: 24, range: 4–90) in responders and 31.6 ± 24.3 (median: 26.5, range: 4–113) in non-responders (P>0.05), respectively.

Remission rates with AZA therapy

Response to therapy with EMH and steroid-free remission was achieved by 37% (44/120) of biologic naive IBD patients after at least 16 weeks of AZA therapy, as shown in Table 1. Response was seen in 42% (19/45) of UC patients, and 33% (25/75) of CD patients. Patients who achieved EMH remained in endoscopic remission during followup, up to a total of 113 months.

Surgical intervention rates were reduced in those patients who responded to AZA therapy, from 18.4% to 4.5% in patients who achieved EMH with AZA (p=0.031). Patients who failed to respond to AZA had a younger age at IBD diagnosis compared to responders (36.1 yrs ± 12.3 vs. 38.1 ± 12.3, P=0.049), and male gender was also significantly associated with a negative response to AZA therapy (72.2% vs. 27.8%, p=0.013), as shown in Table 1.

In patients with CD (75/120) there was no difference between responders and non-responders for smoking rates and Isoniazid use. Azathioprine therapy reduced the number of the surgical interventions in patients with CD, but without a statistical significance as shown in Table 2. There was no difference for the EMH rates in CD group by gender.

Of the 50 patients with CD who failed to respond to AZA, 33 patients were managed with biologic therapy (Table 2). EMH was achieved in 30% of this subgroup treated with biologic therapy at 12 month follow-up. EMH rates were 50% in those patients diagnosed <2 years, vs. 26% in patients diagnosed >2 years.
Discussion

Azathioprine (AZA) is a purine analogue that competitively inhibits the biosynthesis of purine nucleotides, and is widely available as an immunosuppressant at relatively low cost [5–9]. Side-effects of therapy can include leucopenia, pancreatitis, fever and rash, which can sometimes limit their use in clinical practice. However, use and efficacy of AZA in IBD maintenance has been validated as in clinical trials and meta-analyses [2,9–12]. Azathioprine is a standard therapy for moderately or severely active IBD in many countries, particularly in middle to low-income countries. Biologics and now biosimilars are increasingly used in IBD, but with higher drug costs and health-system infrastructure implications that limits availability in many countries [13]. There is a paucity of data on EMH responses with AZA in Asia, and whilst IBD phenotype and complication risks seem unchanged between Asian and White-Western populations, there are heterogeneities between population groups (including genetic susceptibility), that make it important to improve our understanding of AZA efficacy in diverse IBD populations [6]. Therefore, we evaluated the role of AZA to achieve EMH in biologic naive patients with IBD, as well as identify EMH responses in those members of our CD patient cohort who were able to receive biologics therapy in our centre.

Although clinical symptoms and quality of life are the key treatment indicators for patients, we chose mucosal healing as the primary treatment end-point of our study given the increasing recognition of its role by IBD physicians [1,4]. There are several problems with using EMH in clinical studies, including that mucosal healing may not always be achieved, and that clinical response and mucosal healing may not correlate [1,3,7,14–16]. However, overall EMH is correlated with better and prolonged steroid-free remission, and understanding EMH responses across diverse population groups with standard and newer biologic therapies remains important.

We showed that AZA therapy induced EMH in 42.2% (19/45) of severe-active UC patients, and 33.3% (25/75) of moderately-active CD patients who were naïve to biologic therapies in our Turkish cohort. AZA response was associated with statistically significant reduction in surgical interventions in these patients (p=0.031), in keeping with previous reports [17]. Negative predictive factors of response to AZA included a younger age at IBD diagnosis age, and male gender (p=0.049 and p=0.013 respectively). The main limitations of our study include its retrospective nature, and the relatively small number of patients eligible for study inclusion.

Reported EMH rates with AZA and biologic therapy vary between published studies, but our results are similar to previous reports. A randomized controlled trial of AZA compared to 5-ASA for steroid-dependent, moderate or severe UC reported endoscopic remission in 53% of AZA patients, with a recent randomized study of IFX compared to AZA reporting endoscopic mucosal healing in 36.8% receiving AZA alone, also at week 16 [13,17,18].

Evidence for EMH in CD is limited for both AZA and biologic therapies including Infliximab (IFX) [14–21], with differences in published methodology and outcome measures [20,21]. A recent post-hoc analysis of the SONIC study showed EMH rates in 16% of
patients treated with AZA monotherapy at 26 weeks, compared to 30% in those patients treated with IFX [16]. However, this is lower than reports achieved from earlier studies of AZA, with EMH noted in up to 73% of CD patients (mean duration of AZA therapy 24.4 +/- 13.7 months) [21].

Most of these studies are based on White-Western populations, and of the few comparative studies available in Asia, complete or near EMH was achieved with AZA in 25% (9/36) of small bowel CD patients at 12 months, and 56% (20/36) of CD patients at 24 month follow-up with AZA therapy [14].

Overall, there are inconsistencies in EMH rates between different studies that are likely to relate to heterogeneity in study design, drug dosing and disease severity [1,4,5,20,21,14]. These differences preclude direct study and population comparisons, but EMH rates identified in our Turkish IBD cohort seem comparable to other (predominately Western) populations.

In conclusion, our understanding of the efficacy of AZA in diverse IBD population groups is of significance given the important role that this agent plays in many non-high income countries. Our study highlights the efficacy of AZA in achieving EMH in biologic naïve severe-UC and moderate-CD patients, and suggests a younger age at diagnosis and male gender as being negative predictors of AZA mucosal-healing response.

Acknowledgments

Financial Support

Supported by AbbVie, UCB, Pfizer and Takeda to Dr. Atilla Ertan. Professor Aftab Ala is supported by the Clinical Research Network, National Institute for Health and Research (NIH) with Grant Numbers R01 DK054254, R01 DK083850 and R01 HL112248 (to Sonia M. Najjar).

References


Table 1

Characteristics of selected inflammatory bowel diseases patients before and during the azathioprine treatment. Responder means patients with endoscopic mucosal healing; non-responder means patients with no endoscopic mucosal healing.

<table>
<thead>
<tr>
<th>Measured</th>
<th>In IBD group</th>
<th>Responder</th>
<th>Non responder</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of the patients</td>
<td>120 patients</td>
<td>37% (44 patients)</td>
<td>63% (76 patients)</td>
<td></td>
</tr>
<tr>
<td>Patients with CUC</td>
<td>37.50% (45 patients)</td>
<td>42.20% (19 patients)</td>
<td>57.8% (26 patients)</td>
<td>P=0.328</td>
</tr>
<tr>
<td>Patients with CD</td>
<td>62.50% (75 patients)</td>
<td>33.30% (25 patients)</td>
<td>66.70% (50 patients)</td>
<td></td>
</tr>
<tr>
<td>% male in IBD</td>
<td>60% (72 patients)</td>
<td>27.80% (18 patients)</td>
<td>72.20% (54 patients)</td>
<td>P=0.013 a</td>
</tr>
<tr>
<td>Age at the IBD diagnosis (years)</td>
<td>36.9 ± 12.3 (median:36.5, range: 11–72)</td>
<td>38.1 ± 12.3 (median: 39.5, range: 17–58)</td>
<td>36.1 ± 12.4 (median: 35, range: 11–72)</td>
<td>P=0.049 a</td>
</tr>
<tr>
<td>Duration, prior to the azathioprine therapy (months)</td>
<td>39.8 ± 52.5 (median: 24, range: 0–264)</td>
<td>56.2 ± 69.2 (median: 24, range: 0–264)</td>
<td>30.4 ± 37.1 (median: 17.5, range: 0–204)</td>
<td>P=0.147</td>
</tr>
<tr>
<td>Duration of azathioprine used (months)</td>
<td>31.5 ± 24.7 (median: 25.5, range: 4–113)</td>
<td>31 ± 5.7 (median: 24, range: 4–90)</td>
<td>31.7 ± 24.3 (median: 26.5, range: 4–113)</td>
<td>P=0.933</td>
</tr>
<tr>
<td>IBD related surgery % prior to the azathioprine therapy</td>
<td>20% (24 patients)</td>
<td>33.30% (8 patients)</td>
<td>66.70% (16 patients)</td>
<td>P=0.705</td>
</tr>
<tr>
<td>IBD related surgery % during the azathioprine therapy (intestinal resection)</td>
<td>13.30% (16 patients)</td>
<td>12.50% (2 patients)</td>
<td>87.50% (14 patients)</td>
<td>P=0.031 a</td>
</tr>
</tbody>
</table>

P<0.05 was statistically significant. IBD: Inflammatory bowel diseases; CUC: Chronic ulcerative colitis; CD: Crohn’s disease.
Table 2
Results of 75 biologic naive patients with Crohn’s disease by azathioprine therapy.

<table>
<thead>
<tr>
<th></th>
<th>Number of the patients %</th>
<th>Responder</th>
<th>Non responder</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy of azathioprine in previously not-operated patients with Crohn’s disease</td>
<td>70.7% (53 patients)</td>
<td>34% (18 patients)</td>
<td>66% (35 patients)</td>
<td>P=0.858</td>
</tr>
<tr>
<td>Efficacy of azathioprine in previously Crohn’s disease related surgery patients</td>
<td>29.3% (22 patients)</td>
<td>31.8% (7 patients)</td>
<td>68.2% (15 patients)</td>
<td>P=1.000</td>
</tr>
<tr>
<td>(% rate of non-smoking</td>
<td>32 patients (42.7%)</td>
<td>34.4% (11 patients)</td>
<td>65.6% (21 patients)</td>
<td>P=0.98</td>
</tr>
<tr>
<td>Crohn’s disease related surgery need during the azathioprine therapy</td>
<td>17.3% (13 patients)</td>
<td>15.4% (2 patients)</td>
<td>84.6% (11 patients)</td>
<td>P=0.198</td>
</tr>
</tbody>
</table>