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When Should Thiopurine Therapy During Sustained Remission in Inflammatory Bowel Disease be Stopped?

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Abstract

Azathioprine is effective for maintenance of remission in inflammatory bowel disease, nonetheless, duration of efficacy and the dose response relationship has not been fully evaluated. Currently, there are no general recommendations yet that can help us selecting patients who would benefit from the discontinuation of TP without an increased relapse risk.

Keywords: Immuno suppression; Thiopurines; Azathioprine; Inflammatory bowel disease

Abbreviations: AZA: Azathioprine; IBD:Inflammatory Bowel Disease; CD: Crohn`s Disease; UC: Ulcerative Colitis; anti-TNF: Anti-Tumour Necrosis Factor

Introduction

Azathioprine (AZA) have been used in clinical practice for more than 50 years and remain the mainstay of maintenance treatment for inflammatory bowel disease (IBD), either as alone and/or in combination with anti-tumour necrosis factor (anti-TNF) drugs [1]. Today, Thiopurine have demonstrated their capacity maintaining remission in the long-term in both Crohn`s disease (CD) [2,3] and ulcerative colitis (UC) [4,5], and it seems that the effect does not disappear after for up to 5 years [6]. Moreover, during follow-up responders had a significantly reduced risk of intestinal surgery and perianal surgery [7].

Discussion

Despite increasing evidence of safety from several studies, a percentage of responders developed cancers, including non-melanoma skin cancers [7,8]. A rare and usually fatal lymphoma, hepatosplenic T-cell lymphoma, has been related with younger IBD patients who received long-term therapy (at least 2 years) with Thiopurine [9]. Thiopurine use in IBD appears to be strongly related with an increased risk of Epstein-Barr virus-positive lymphoma [10,11]. Recently, it has been linked immunosuppressive treatment with opportunistic infections during severe lymphopenia in IBD patients [12]. Regular monitoring of blood counts and liver test is required in order to early detection of bone marrow and liver toxicities [13,14].

Treatment strategies have changed accordingly. Presently, the early introduction of Immuno modulators and anti-TNF therapy targeting a window of opportunity before the development of potentially intestinal complications and they are capable of change the disease evolution. However, the clinicians unknown the best moment of therapy stopping once remission is achieved. Identifying IBD patients with increased risk of relapse after Thiopurine withdrawal during sustained clinical remission is essential for appropriate management.

From a clinical point of view, our patients are young and have a long life expectancy. Physicians should consider maintaining thiopurinesonly in cases in which a clear benefit is expected. On the other hand, whether or not AZA can be stopped is an important question and factors involved in the decision to removal the drug in patients with IBD are necessary. Previous retrospective study suggested that the risk of relapse appeared to be similar if we withdrawal or maintain AZA after 4 years of remission in CD patients [15]. In Table 1 you can see the most relevant studies assessing relapse rate in IBD patients under

immuno suppressive therapy in case of discontinuation as well as the predictive factors.

Table 1: Summary of AZA/MP withdrawal studies.

Study	Desing study	N	Drug	UC/ CD	Duration of Thiopurine (Months)	Follow up (Months)	Relapserate	Factors Redictive of Relapse
Peter S Kim et al. [16]	Clinical trial Prospective Unicentric	120	6-MP	CD	6	6-150	With 6MP: 32 months Without 6MP: 16 months	- Young people-More time with treatment before withdrawal
M Vilien [17]	Clinical Trial Prospective Unicentric	29	AZA	CD	24	12	With AZA 11 months Without AZA 9 months	
Marc Léman [18]	Clinical trial Prospective Multicentric	83	AZA	CD	42	18	With AZA 17 meses Without AZA 15 months	-CRP> 20 mg/L-Time without steroids > 50 months- Hemoglobin< 12 g/dL
Andrea Cassinotti [19]	Observational Retrospective Multicentric	127	AZA	UC	47	55	1 year (35%) 2years (49%) 5 years(60%)	-Extense colitis-more time with aza before withdrawal
Xavier Treton [20]	Observational Prospective Unicentric	66	AZA	CD	42	18	28 without AZA	- CPR>de 20 -leukocytosis -hemoglobin< de 12 g/dL
N A Kennedy [21]	Observational Retrospective Retrospective Multicentric	237	AZA	UC and CD	720	12 and 24	1 year: 23 % CD and 39% UC 2 yeras: 12%CD y 26 % UC 2 yeras: 12%CD y 26 % UC	-CPR>20 -leukocytosis -extension-emoglobin< 12g/dl
Estefanía Moreno Rincón [22]	Observational Retrospective Multicéntric	102	AZA	UC	51	12, 36, and 60	12 monthswithout AZA	- time without steroids - Hemoglobin<12 g/dL - extension, -time to diagnosis until AZA treatment
HeimoH.Wenzl [23]	Ensayo clínico Prospectivo multicéntrico	52	AZA	CD	48	24	With AZA 22 months Without AZA 19 months	- Young people -Time without steroids - Remision< 4 años - Hemoglobin<2 g/dL - Leucocitosis y PCR

AZA (Azathioprine), 6-MP (6 mercaptopurine), CPR (C reactive protein), UC (ulcerative colitis), CD (Crohn`s disease)

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Conclusion

In conclusion, Thiopurine withdrawal in the context of sustained remission is associated with a high risk of relapse. Currently discontinuation of AZA may be considered after 4 years in IBD patients in sustained remission and steroid free [24,25]. Further investigations are necessary in order to identify risk factors of relapse after stopping immunosuppressive therapy. The safety and actual risk/benefit ratio of therapy withdrawal needs to be studied in prospective controlled trials, given the need to optimize the use and duration of potentially risky and costly therapies.

Conflict of Interest

No financial support was received for the preparation of this study. The authors declare that no conflict of interest exists.

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