Azathioprine and erythema nodosum

Introduction

Azathioprine (Azafalk®, Azathioprine®, Imuran®) is an immunosuppressive antimetabolite that is indicated for the treatment of *Crohn's disease*, *ulcerative colitis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, autoimmune chronic active hepatitis, pemphigus vulgaris, polyarteriitis nodosa, autoimmune hemolytic anemia and chronic refractory idiopathic thrombocytopenic purpura* [1]. Azathioprine is an imidazolyl derivate of 6-mercaptopurine. 6-mercaptopurine works as a purine antagonist that is intracellularly anabolized into tioguanine nucleotides. These nucleotides and other metabolites inhibit de novo purine synthesis and interconversions of purine nucleotides, and contribute to an immunosuppressive reaction via their incorporation in nucleic acids. Another potential mode of action is the inhibition of different routes in the synthesis of nucleic acids, resulting in the inhibition of the immune response [1]. Azathioprine has been authorized for marketing since 1968.

Erythema nodosum (EN) is a cutaneous disorder that is characterized by tender red nodules, commonly on the shins of the lower legs, and without the formation of pus. The nodules disappear spontaneously within three to six weeks and resolve without residual scarring. However, the nodules can return after a period of time [2]. EN can be triggered by exposure to drugs and micro-organisms, but can also occur in combination with systemic diseases [3]. EN is estimated to occur in up to 15% of patients with Crohn's disease [4], and is linked to an increased disease activity of inflammatory bowel disease [5]. EN is more common in women than in men, and mostly arises in early adulthood [3].

Reports

In the period from July 2011 to December 2019 the Netherlands Pharmacovigilance Centre Lareb received four reports of EN in association with the use of azathioprine (L04AX01). The reports are listed in Table 1.

Table 1: Reports of erythema nodosum associated with administration of azathioprine in the Lareb database

No	ID, sex, age, primary source	Drug	Dosage	Indication	Concomitant medication	Reported ADRs	Latency after start	Action taken	Outcome
1	NL-LRB-124729, F, 49Y, Dermatologist	Azathioprine	50 mg	Crohn's disease		Erythema nodosum	3 Weeks	Drug Withdrawn	Recovered
2	NL-LRB-137284, F, 45Y, Medical Specialist	Azathioprine	100 mg/ 1 Days	Crohn's disease	Budesonide Polyethylene glycol	Fever Liver enzyme abnormal Erythema nodosum	14 Days	Drug Withdrawn	Recovered
3	NL-LRB-00367871, F, 22Y, Other healthcare professional	Azathioprine	50 mg/ 12 Hours	Crohn's disease	Budesonide Prednisone	Erythema nodosum Fever	19 Days	Drug Withdrawn	Recovered
4	NL-LRB-00367983, F, 49Y, Physician	Azathioprine	200 mg/ 1 Days	Crohn's disease	Methotrexate	Flu like symptoms Erythema nodosum	19 Days	Unknown	Recovered

Other sources of information

SmPC

EN is not listed in paragraph 4.8 of the Dutch SmPC of azathioprine. Hypersensitivity reactions are mentioned, but not specified [1].

Literature

In literature, there are a handful of case reports on drug-induced EN after administration of azathioprine (Table 2). Six cases concerned patients with Crohn's disease, whereas two cases concerned patients with respectively bullous pemphigoid and chronic idiopathic urticaria. In all cases, the skin lesions appeared within three weeks after azathioprine initiation, and recovered within three

weeks after discontinuation of azathioprine. After rechallenge, the skin lesions returned within hours to four weeks. In two cases, EN was accompanied by a flare or progression of Crohn's disease [6, 7], whereas the role of an IBD flare was dispelled in another case [8]. In the other cases, the role of a potential IBD flare was not mentioned.

Table 2: Literature cases of EN and azathioprine.

Reference	Sex, age	Indication	Latency	Time to recovery	Rechallenge
Cheraghi et al. **[9]**	F, 58Y	Crohn's disease	6 days	6 days	N/A
González-Olivares et al. **[7]**	F, 44Y	Crohn's disease	21 days	3 days	N/A
De Fonclare et al. **[6]**	F, 17Y F, 49Y M, 75Y	Crohn's disease Crohn's disease Crohn's disease	14 days 8 days 14 days	16 days 12 days 14 days	Positive, within 12 hours Positive, within 4 hours N/A
Ross et al. **[8]**	M, 13Y	Crohn's disease	Unknown	Unknown, but patient did recover	Positive, within 4 weeks
Vargas-Hiltos et al. **[10]**	F, 65Y	Bullous pemphigoid	1 week	14 days	N/A
Wang et al. [11]	F, 37Y	Chronic idiopathic urticaria	14 days	6 days	N/A

F: Female; M: Male.

Other databases

Table 3: Reports of PT Erythema nodosum associated with azathioprine in the Lareb, WHO and Eudravigilance database [12, 13].

Database	Number of reports	ROR (95% CI)
Lareb	4	9.5 [3.5-25.9]
WHO[a]	94	14.1 [11.5-16.7]
Eudravigilance[a]	70	13.0 [10.2-16.4]

[a]Including the reports received by Lareb.

In Eudravigilance, 70 reports were received of erythema nodosum in association with azathioprine [13]. These reports included three supporting literature cases that were sent to Eudravigilance after December 2018. One case described a 13-year-old patient with Crohn's disease that developed EN after azathioprine initiation, while the patient's gastrointestinal symptoms were well-controlled [8]. Secondly, a 37-year-old female with chronic idiopathic urticaria presented EN and hepatotoxicity two weeks after azathioprine initiation. Azathioprine was discontinued and EN subsided six days later [11]. The third case described a 46-year-old male with ulcerative colitis. EN developed approximately 1.5 week after azathioprine initiation. The lesions recovered after discontinuation of azathioprine treatment [case 2019FE05629].

Prescription data

Table 4: Number of patients using azathioprine in the Netherlands between 2014 and 2018 [14].

Drug	2014	2015	2016	2017	2018
Azathioprine	27.622	27.949	28.079	26.866	26.153

Mechanism

EN can be triggered by various causes, including Crohn's disease and the exposure to certain drugs [3]. EN is thought to result from the formation of immune complexes that deposit around and in venules that surround subcutaneous fat, and is histopathologically characterized by a neutrophilic inflammatory infiltrate located at the subcutaneous septa [15]. In literature, EN is often mentioned as a hypersensitivity response [6, 7, 9, 10].

The exact mechanism of azathioprine hypersensitivity is still unclear, but there are various hypotheses. In one study, it was described that the imidazole component of azathioprine is partly responsible for azathioprine hypersensitivity [16]. In contrast, another study showed that 6-mercaptopurine resulted in similar manifestations of hypersensitivity to azathioprine [6]. Lastly, *NUDT15* polymorphism was described as a potential predisposing factor of azathioprine hypersensitivity [11].

Discussion and conclusion

Lareb received four reports of EN in association with the use of azathioprine. Furthermore, the association between EN and azathioprine is disproportionally present in the databases of Lareb, Eudravigilance and the WHO. Supporting case reports were also found in literature.

EN can be triggered by various factors, including Crohn's disease, and has been linked to an increased disease activity [5]. Therefore, the association of EN and azathioprine is challenged by confounding by indication, since the reports of Lareb concern patients with Crohn's disease. Despite the underlying bias, it was demonstrated in literature that EN can also develop without the presence of a flare or an imbalance of gastrointestinal symptoms [7, 8]. These literature cases are also present in Eudravigilance. Likewise, no relation between the disease activity and EN was mentioned in the cases reported to Lareb.

In the case reports in literature and in cases reported to Lareb, EN appeared within three weeks after azathioprine initiation. All literature reports recovered within three weeks after discontinuation of azathioprine, and positive rechallenges have been reported after azathioprine discontinuation [6-10]. Given the appearance of EN shortly after azathioprine initiation, the rapid recovery after azathioprine discontinuation and the relapse after azathioprine rechallenge, EN is hypothesized as an hypersensitivity reaction to azathioprine [6, 7, 9, 10]. Therefore, attention for this potential adverse drug reaction is warranted.

References

1. Dutch SmPC Imuran®. 07-11-2019.
2. Erythema nodosum [Internet]. UpToDate. 2020 [cited 13-7-2020]. Available from: https://www.uptodate.com/contents/erythema-nodosum.
3. Rubin R, Strayer D. Rubin's Pathology. Clinicopathologic Foundations of Medicine 6ed. Baltimore, MD: Lippincott Wolters Kluwer; 2012.
4. Trikudanathan G, Venkatesh PG, Navaneethan U. Diagnosis and therapeutic management of extra-intestinal manifestations of inflammatory bowel disease 2012 [updated Dec 24. 2012/11/28:[2333-49].
5. White JW, Jr. Erythema nodosum. Dermatol Clin. 1985;3(1):119-27.
6. de Fonclare AL, Khosrotehrani K, Aractingi S, Duriez P, Cosnes J, Beaugerie L. Erythema nodosum-like eruption as a manifestation of azathioprine hypersensitivity in patients with inflammatory bowel disease. Arch Dermatol. 2007;143(6):744-8.
7. González-Olivares M, Khedaoui R, Martínez-Morán C, Borbujo J. Azathioprine-Induced Hypersensitivity Reaction Presenting as Erythema Nodosum. Actas Dermosifiliogr. 2017;108(6):591-3.
8. Ross R, Miller R. Erythema nodosum due to azathioprine in a 13-year-old male with Crohn disease Clinical Dermatology and Other Cutaneous Disorders. 2010;62(3):1114.
9. Cheraghi N, Yasuda M, Deng A, Mailhot J. Azathioprine hypersensitivity presenting as neutrophilic dermatosis and erythema nodosum. Cutis. 2016;98(1):E7-9.
10. Vargas-Hitos JA, Sabio JM, Tercedor J, Navarrete-Navarrete N, Jiménez-Alonso J. Erythema nodosum as azathioprine hypersensitivity reaction in a patient with bullous pemphigoid. Indian J Dermatol. 2013;58(5):406.
11. Wang CH, Chi MH, Lin JY, Chung WH, Chen CB. NUDT15 polymorphism identified in a patient with azathioprine hypersensitivity syndrome presenting as erythema nodosum and hepatotoxicity. Br J Dermatol. 2019;181(3):631-2.
12. WHO Global Individual Case Safety Reports database (Vigilyze) [Internet]. 2020 [cited 27-05-2020]. Available from: https://tools.who-umc.org/webroot/ (access restricted).
13. Eudravigilance database [Internet]. European Medicines Agency. 2020 [cited 27-05-2020]. Available from: http://bi.eudra.org (access restricted).
14. GIP Databank [Internet]. 2019 [cited 18-06-2020]. Available from: https://www.gipdatabank.nl.
15. Requena L, Requena C. Erythema nodosum. Dermatol Online J. 2002;8(1):4.
16. McGovern DP, Travis SP, Duley J, Shobowale-Bakre el M, Dalton HR. Azathioprine intolerance in patients with IBD may be imidazole-related and is independent of TPMT activity. Gastroenterology. 2002;122(3):838-9.