

Tioguanine (Thiosix®) and alopecia

Introduction

Tioguanine is an analogue of guanine and acts as a purine antimetabolite. Its metabolites inhibit de novo purine biosynthesis and purine nucleotide conversions. Tioguanine nucleotides (6-TGN) are incorporated into both DNA and RNA, which attributes to tioguanine cytotoxicity. In The Netherlands, tioguanine is available for two different purposes. Lanvis® (tioguanine, 40 mg) is indicated for treatment of *acute myeloid leukaemia and acute lymphatic leukaemia* [1]. Since 2015, Thiosix® (tioguanine, 10 and 20 mg) has been available with conditional approval, indicated for *maintenance therapy of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) in patients who are intolerant or do not respond to standard thiopurine treatment with azathioprine and 6-mercaptopurine* [2]. Tioguanine metabolism differs from azathioprine and 6-mercaptopurine, resulting in higher concentrations of active 6-TGN metabolites and less metabolites from the thiopurine-S-methyltransferase (TPMT) pathway that correlate with azathioprine/mercaptopurine liver and bone marrow toxicity [3, 4].

There are two main types of drug-induced alopecia: anagen effluvium (shedding of growing hairs with the use of cytotoxic drugs) and telogen effluvium (shedding of resting hairs with the use of various drugs and other causes). Anagen effluvium is caused by damage to hair matrix cells since these are dividing cells vulnerable to DNA toxicity. Alopecia with chemotherapy occurs within days to weeks of starting chemotherapy. Telogen effluvium usually occurs two to four months after start of the offending drug [5, 6]. It is a result of an abnormal shift in follicular cycling of hairs, in which growing hairs from the anagen phase enter the telogen phase prematurely and shed. The mechanism is unclear [7].

Reports

From December 2004 until February 2019 the Netherlands Pharmacovigilance Centre Lareb received 20 reports of alopecia associated with the use of tioguanine indicated for Crohn's disease or ulcerative colitis. There are no reports of alopecia associated with the use of tioguanine for other indications. The reports are summarized in table 1.

Eleven reports were directly reported to Lareb, whereas nine reports were reported via Marketing Authorization Holders (MAH's). In three reports tioguanine 40 mg (brand Lanvis® or unspecified) was used, the other reports concerned tioguanine doses from 5 to 25 mg (brand Thiosix® or unspecified).

Table 1. Reports of tioguanine associated with alopecia in the Lareb database

| Patient, Sex, Age (years) | Suspect drug(s) Indication for use | Concomitant medication | Suspected adverse drug reaction [description from reporter] | Time to onset, Action with drug Outcome |
|---|---|---|--|---|
| [A] NL20060038 MAH, Physician F, 21-30 | Azathioprine 50mg 150mg per 1.0 d Crohn's disease Lanvis tablet 40mg Unspecified indication | Ferrofumarate Hydroxocobalamine | Alopecia [alopecia] Lymphopenia Malaise Arthralgia Pregnancy / normal birth | 3 months Unknown Unknown |
| [B] NL-LRB-00264904 Pharmacist F, 31-40 | Thiosix tablet 20mg Crohn's disease 20.00 mg per 1.0 d | Omeprazole Mesalazine Sulfasalazine Levonorgestrel iud Prednisolone | Alopecia [hair loss] Pneumonia Fever Dyspnoea Cough | Unknown Dose not changed Unknown |
| [C] NL-LRB-00311565 Consumer F, 41-50 | Thiosix tablet 20mg Crohn's disease 25.00 mg per 1.0 d | Tramadol Calciumcarbonate/ colecalciferol Omeprazole | Alopecia [extreme hair loss with irritation of scalp] | 3 weeks Dose not changed Not recovered/not resolved/ongoing |
| [D] NL-LRB-237709 Consumer F, 41-50 | Tioguanine tablet 20mg Crohn's disease 20.00 mg per 1.0 d | Multivitamines | Alopecia Madarosis [severe hair loss including eyelashes, no visible boldness] | 1 month Drug withdrawn Recovering/resolving |

| Patient, Sex, Age (years) | Suspect drug(s) Indication for use | Concomitant medication | Suspected adverse drug reaction [description from reporter] | Time to onset, Action with drug Outcome |
|--|---|---|---|--|
| [E] NL-LRB-47516 Consumer F, 31-40 | Lanvis tablet 40mg 20.00 mg per 1.0 d Ulcerative colitis | Mesalazine Calcium gluconate | Alopecia [hair loss/ matt/ lifeless] Chills Headache Arthralgia | Unknown (shortly) Drug withdrawn Recovered/resolved |
| [F] NL-LRB-201256 Consumer F, 31-40 | Aces-tg tablet 10mg - Crohn's disease 10.00 mg per 1.0 d | | Alopecia [hair loss, thinner hair, less new hairs] | 3 months Dose not changed Not recovered/not resolved/ongoing |
| [G] NL-TEVA-2018-NL-957585 MAH, Physician, M, 41-50 | Thiosix tablet 20 mg Inflammatory bowel disease | | Hair loss [hair loss] | 1 day Dose not changed Unknown |
| [H] NL-TEVA-782383ROM Physician F, 41-50 | Tioguanine 25 mg teva Inflammatory bowel disease | Prednisone Macrogol | Hair loss [loss of hair] Fatigue | 15 days Drug withdrawn Recovered/resolved |
| [I] NL-LRB-00279117 Consumer F, 51-60 | Lanvis tablet 40mg Crohn's disease 20.00 mg per 1.0 d | | Alopecia [severe hair loss] Arthritis | 2 weeks Dose not changed Not recovered/not resolved/ongoing |
| [J] NL-LRB-130402 Physician F, 31-40 | Lanvis tablet 40mg Crohn's disease Adalimumab 50 mg/ml | Acenocoumarol | Alopecia [hair loss] | 2 weeks Dose not changed Not recovered/not resolved/ongoing |
| [K] NL-LRB-189383 Physician F, 11-20 | Lanvis tablet 40mg product used for unknown indication Adalimumab 50 mg/ml Crohn's disease | Non specified oac | Hair loss [and progressive hair loss] Papulopustular rash Psoriasis | Days Not applicable Recovering/resolving |
| [L] NL-TEVA-2017-NL-830036 MAH, Physician F, 41-50 | Thiosix 20 mg Inflammatory bowel disease 20.00 mg per 1.0 d Vedolizumab | | Accelerated hair loss [increasing loss of hair] Fatigue aggravated Ankles swollen Vesicular rash Finger cramps Inner ear inflammation Body temperature increased Drug specific antibodies | 8 months Dose not changed Recovered/resolved |
| [M] NL-TEVA-2018-NL-848167 MAH, Physician F, 51-60 | Thiosix 20 mg Inflammatory bowel disease | | Hair loss [loss of hair, severe] | 2 months Drug withdrawn Recovered |
| [N] NL-TEVA-785243ROM Physician F, 31-40 | Thiosix 10 mg inflammatory bowel disease 5 mg per day, 10.00 mg every other day | Adalimumab Folic acid | Hair loss [surely loss of hair recently] | Unknown Drug withdrawn Recovered/resolved |
| [O] NL-LRB-00303921 Consumer F, 31-40 | Tioguanine tablet 10mg Colitis ulcerative 10.00 mg per 1.0 d | Mesalazine Cyproteron/ Ethinylestradiol | Alopecia [hair loss; tufts of hair at once] | 20 days Unknown Not recovered/not resolved/ongoing |

| Patient, Sex, Age (years) | Suspect drug(s) Indication for use | Concomitant medication | Suspected adverse drug reaction [description from reporter] | Time to onset, Action with drug Outcome |
|---|--|---|--|---|
| [P] NL-LRB-207181 Pharmacist F, 21-30 | Aces-tg tablet 20mg - non-current drug Colitis ulcerative 20.00 mg per 1.0 d | Calcium, Mesalazine, budesonide, lidocaine, ciprofloxacin, prednisolone, levonorgestrel and estrogen, Isosorbide dinitrate, pantoprazole, levocetirizine, triamcinolone, paracetamol | Alopecia [severe hair loss] | 2 months Dose reduced Not recovered/not resolved/ongoing |
| [Q] NL-LRB-230519 Consumer F, 21-30 | Tioguanine tablet 20mg Crohn's disease 20.00 mg per 1.0 d | Infliximab | Alopecia [hair loss: easily shedding with follicles, thinner hair] Rash facial | Weeks Dose not changed Not recovered/not resolved/ongoing |
| [R] NL-TEVA-2018-NL-844351 Physician F, 41-50 | Tioguanine tablet 20mg Inflammatory bowel disease | | Hair loss [hair loss] | 4 months Unknown Recovered/resolved |
| [S] NL-TEVA-2018-NL-868675 Physician F, 21-30 | Tioguanine 10 mg Inflammatory bowel disease Ferrofumarate 600 mg Anaemia | | Hair loss [more hair loss] Headache Fatigue | 3 months Unknown Recovered/resolved |
| [T] NL-TEVA-2018-NL-963701 Physician F, 21-30 | Tioguanine Inflammatory bowel disease | Infliximab Oral contraceptive Salbutamol Fluticasone /salmeterol Paracetamol | Hair loss [hair loss since start thiosix] | 1 day Drug withdrawn Unknown |

Additional information on reports:

[A] No specific description of alopecia. Main suspect drug was azathioprine. Concomitant medication indicates anemia.

[B] No specific description of alopecia. One month after start and shortly after dose increase of tioguanine the patient developed pneumonia with fever. With follow up information, 3 months later, it was mentioned that the patient also had developed hair loss from an unspecified date.

[C] Description of alopecia: extreme hair loss with irritation on scalp. Crohn's disease for two years and previously treated with azathioprine, methotrexate, prednisolone, budesonide. Never had hair loss before. No concurrent illness in the past months.

[D] Diffuse hair loss and easy shedding from hairs by touching scalp and lots of broken hairs. Less hair loss with lower doses of tioguanine and worse after dose increase. After withdrawal of tioguanine, the patient only had a little bit of hair loss remaining. The patient was not menopausal.

[E] Description: dull lifeless hair with hair loss. Starting shortly after start tioguanine, recovered after withdrawal after a 3 to 4 year period of use.

[F] Description: hair loss, thinner hair, less new hairs.

[G] Description: hair loss, reported as a mild adverse event on a visit after 15 months with start date of hair loss as the same start date of tioguanine. Medical history includes esophageal reflux, keratitis, spondylarthrosis, COPD, uveitis, intermittent mouth ulcers.

[I] Description: severe hair loss, the patient feared that continuing tioguanine results in baldness.

[J] No specific description of hair loss. Latency with tioguanine was 2 weeks. Adalimumab as co-suspect drug had been used for 1.5 years.

[K] Serious report with severe skin reaction with main suspect drug adalimumab with a latency of 3 months. Single dose of Lanvis® administered during skin reaction period, after which skin reaction aggravated and a few days later progressive hair loss occurred. Patient had been treated with prednisone and betamethasone for skin reaction. After withdrawal of adalimumab, azathioprine was started, which induced acute pancreatitis.

[L] Crohn's disease for eleven years. Increasing loss of hair from February until September, starting 8 months after start of tioguanine. Recovered after unknown period while the dose for tioguanine was maintained.

[O] Description: large tufts of hair loss at once.

[P] Description: severe hair loss, very stressing for a 21-30 year old female.

[Q] Description: Diffuse hair loss; hairs shed easily with hair follicles, hairs appear to be thinner as well. Scalp is normal according to dermatologist.

[S] No specific description of alopecia. Patient also had anemia.

Clinical pattern of alopecia in the reports

Times to onset of alopecia varied from one month or less in eleven reports, to two to three months in five reports and more than 4 months in 2 reports.

In five reports, the patients recovered from hair loss after withdrawal of tioguanine, with times to recover of days to four weeks (as was reported in three reports). In one report [D] a dose relationship was experienced. In five reports, the dose for tioguanine was not changed and alopecia had not resolved.

Descriptions of hair loss, present in part of the reports, varied from diffuse hair loss, broken hairs, lack of new hair growth and thinner hairs.

In ten reports concomitant medication that is known to be able to cause alopecia has been used. In five reports comorbidity may have influenced the occurrence of alopecia, such as acute illness with fever (B), multiple autoimmune diseases (G), Lyme disease (M) and anemia (A, S).

Other sources of information

SmPC

The Summary of Product Characteristics (SmPC) of tioguanine (10 mg and 20 mg, Thiosix®) does not mention alopecia as an adverse drug reaction. The SmPC of tioguanine (40 mg, Lanvis®) warns for an increased risk of severe tioguanine toxicity, such as early leukopenia and alopecia, in conventional doses in patients with inherited mutated *NUDT15* gene [1] [8]. Thiosix® is a medicinal product under additional monitoring [9].

Literature

Bonaz et al. performed an open and prospective study in 49 patients with Crohn's disease, with intolerance or persistence to azathioprine/mercaptopurine with tioguanine 20 mg/day, of whom 1 patient developed an unspecified form of alopecia [10].

Herrlinger studied 6-tioguanine efficacy and safety in chronic active Crohn's disease for inducing remission and in maintenance therapy. In the first study, 37 patients were included and treated with tioguanine 40 mg and three patients developed alopecia. In the second study, 16 patient received maintenance therapy with tioguanine 20-40 mg and one patient developed mild unspecified form alopecia [11, 12]

Patel et al. discuss the concurrence of hair loss in patients with inflammatory disease (IBD). From a literature search they conclude that telogen effluvium has been associated with IBD, either caused by acute illness, nutritional deficiencies due to IBD or by a side effect of medications used to treat IBD [13]. Shah et al. performed a retrospective cross sectional study in a tertiary care hospital on self-reported alopecia in 150 IBD patients. One-third experienced hair loss during their illness, of which two-third reported diffuse and one-third patch like hair loss. In 62% of the cases, hair loss occurred during a flare of IBD illness. Hair loss was less common with patients treated with mesalazine or TNF-alfa inhibiting agents. Hair loss was not related to gender, age, type of IBD and vitamin deficiencies. They conclude that alopecia might be considered as an extra-intestinal manifestation in IBD diseases [14].

More recently, shared genetic factors with alopecia areata and IBD have been identified [13, 15]. A case-report, described by Shohdy et al. refers to a previously undiagnosed ulcerative colitis patient with diarrhoea and alopecia totalis who regained hair growth with azathioprine and mesalazine treatment [16].

Databases

Table 2. Reports of alopecia associated with the use of tioguanine in the Lareb, WHO and Eudravigilance database [17, 18]

| Database | Drug | ADR | Number of reports | ROR (95% CI) |
|----------------|------------|----------|-------------------|----------------|
| Lareb | Tioguanine | alopecia | 20 | 7.3 [4.0-13.4] |
| WHO | Tioguanine | alopecia | 28 | 1.6 [2.4-3.5] |
| Eudravigilance | Tioguanine | alopecia | 20 | 3.3 [1.7-5.9] |

The Eudravigilance (EV) database does not contain any reports, other than the reports also present in the Lareb database. It has to be noted that in the past MAHs were not required to send non-serious reports to EV.

Table 3. Prescription data (users) [19].

| Drug | 2013 | 2014 | 2015 | 2016 | 2017 |
|------------|-------|-------|-------|-------|-------|
| tioguanine | 1,163 | 1,431 | 1,961 | 3,783 | 5,113 |

Mechanism

Tioguanine is a cytotoxic agent that acts like a purine antimetabolite affecting DNA in rapidly dividing cells, including dividing hair matrix cells. Proliferation of keratinocytes in the hair matrix is inhibited. This can result in hair loss by shedding of growing hairs (anagen effluvium) and by thinning of the hair shaft of hairs in resting phase that can break easily [6]. The severity of alopecia depends on the degree of toxicity of the cytotoxic agent.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 20 reports of alopecia with the use of tioguanine indicated for inflammatory bowel diseases. These reports concern one male and nineteen females, with ages varying from 18 to 58 years. In the Lareb database in general, alopecia is more often reported in females than males and is considered as a more disturbing reaction in females than in males [20].

A latency shorter than four weeks, as has been reported in eleven reports, of which four had a positive dechallenge, as well as some specific descriptions of hair loss, may suit an anagen effluvium, probably based on the cytotoxic properties of tioguanine. Other reports with longer latencies might be confounded by indication, since various forms of alopecia are associated with IBD due to flares of IBD, concurrent acute illness, nutritional deficiencies or as side effect of various medications [13, 14]. In the Lareb reports, information on flares of IBD were not reported. Alopecia has been described in literature as a few cases in small studies of tioguanine in inflammatory bowel diseases. However, information about type and time to onset of alopecia was not provided in these studies.

Little information on gene mutations considering tioguanine metabolism is described in treatment guidelines. Unlike azathioprine and mercaptopurine, tioguanine is a poor substrate for TMPT [4]. Patients with mutated *NUDT15* gene experience more toxicity with tioguanine and need dose reduction. This has been described with doses over 40-60 mg [1, 21]. Some Dutch treatment guidelines for inflammatory bowel diseases do mention the use of tioguanine, but do not give advice on dose adjustments nor screening for gene mutations [22, 23].

The association of alopecia and tioguanine is supported by a statistically significant disproportionality in databases of Lareb, Eudravigilance and WHO.

Considering the specific time pattern and a pharmacological mechanism of tioguanine that suits anagen effluvium, this signal describes a possible association of alopecia with the use of low dose tioguanine (Thiosix®).

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This signal has been raised on June 6, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl