Adalimumab and menstrual cycle and uterine bleeding disorders

Introduction

Adalimumab is a recombinant human monoclonal antibody that binds specifically to tumour necrosis factor (TNF)-α. By binding to TNF-α it neutralizes TNF-α's biological mechanism of action by blocking the interaction of TNF-α with p55 and p75 TNF receptors. Additionally, adalimumab modulates the biological response that is induced or regulated by TNF-α including adhesion molecule concentrations (ELAM-1, VCAM-1, ICAM-1) required for leukocyte migration [1]. The innovator adalimumab (Humira®) product was granted marketing authorization on 8 September 2003 in Europe [1]. Subsequently, 7 biosimilars have been granted marketing authorization in Europe including: Amgevita® (2017), Imraldi® (2017), Hyrimoz® (2018), Idacio® (2019), Hulio® (2020), and Yuflyma® (2021) [2-7]. Adalimumab is prescribed when insufficient response to conventional therapy is achieved for the following therapeutic indications: *rheumatoid arthritis* (as mono- or combination therapy with methotrexate), *juvenile idiopathic arthritis* (idiopathic arthritis, from 2 years old and enthesis related arthritis from 6 years old), *axial spondyloarthritis*, *psoriatic arthritis* , *psoriasis* (from 4 years old, when not eligible for topical therapy and light therapy), *hidradenitis suppurativa* (from 12 years old)*, Crohn's disease, juvenile Crohn's disease* (from 6 years old)*, ulcerative colitis, uveitis and juvenile uveitis* (from 2 years old) [2].

Other TNF-α inhibitors available on the Dutch market are etanercept (Enbrel®), infliximab (Remicade®), certolizumab pegol (Cimzia®) and golimumab (Simponi®) [8-11].

Menstruation disorders are common and include the absence of bleeding (amenorrhoea), irregular bleeding (oligomenorrhoea), abnormally heavy bleeding (menorrhagia), bleeding in between periods (metrorrhagia) and painful periods (dysmenorrhea) [12]. These definitions are only valid for women who are still menstruating. Incidence and prevalence rates in Dutch general practice are reported in Table 1. Menstruation disorders may have several causes, including but not limited to: medical problems involving the hypothalamic-pituitary-gonad-uterus axis and systemic diseases, such as autoimmune diseases (systemic lupus, erythematosus, celiac disease and inflammatory bowel disease (IBD) [13] and drug use (e.g. methotrexate [14] or corticosteroids [15]).

Table 1. Incidence and prevalence rates of menstruation disorders in Dutch general practice in 2019 (per 1000 patient years) [16].

Complaint	Incidence	Prevalence
Painful menstruation	2.1	4.1
Irregular/infrequent menstruation	3.2	5.6
Intermenstrual bleeding	2.3	3.8
Delayed bleeding	4.1	3.3
Menorraghia	3.7	6.7
Amenorrhoea/hypomenorrhoea/oligomenorrhoea	1.5	2.5

Reports

In the period from November 24th, 2009 to May 25th, 2021 the Netherlands Pharmacovigilance Center Lareb received 13 reports on menstrual cycle and uterine bleeding disorders (HGLT) associated with adalimumab use. 12 of these were spontaneous reports and one report was included from the Lareb Intensive Monitoring (LIM) 'Dutch Biologic Monitor' study, in which patients with a rheumatic disease, psoriasis or inflammatory bowel disease treated with biological medicines were followed over time [17]. All included reports are listed in Table 2.

Table 2. Reports of adalimumab and menstruation and uterine bleeding disorders (HGLT).

No	ID, sex, age, primary source	Drug, dose, Indication	Concomitant medication	Reported ADRs (LLT)	Latency after start Action taken Outcome
1	NL-LRB-94745, female, 40-50 Years, Physician	Humira®(adalimumab) Methotrexate Rheumatoid arthritis	Naproxen	Hyperhidrosis, Haematoma, Menorrhagia	6 Months 6 months 9 months Dose Not Changed

				Also fluctuations of the hormone levels	Not Recovered
2	NL-JNJFOC-20110206671, female, 30-40 Years, Other health professional	Remicade® (infliximab) Humira® (adalimumab)		Excessive menstruation, Bruise, Drug interaction	Unknown
3	NL-LRB-184594, female, 10-20 Years, Physician	Humira®(adalimumab) Rheumatoid arthritis		Irregular menstrual cycle	18 Months Dose Not Changed Not Recovered
4	NL-LRB-206669, female, 40-50 Years, Physician	Humira®(adalimumab) Psoriatic arthritis Medical history: patient had Hypermenorrhea before, but the menstruation was normal for 6 months now, and has Polycystic ovaries. Gynaecologist could not find indications for polycystic ovaries at this moment.	Methotrexate, Naproxen Folic acid, Omeprazole, Hydrochlorothiazide	Menorrhagia, Amenorrhoea	Following administration. The patient recovered from menorrhagia after 9 days, but experienced amenorrhoe from then during 5 months and recovered spontaneously. Then the menorrhagia returned and the patient was treated with medroxyprogesteron and recovered. Dose Not Changed
5	NL-ABBVIE-18K-114-2226674-00, female, 40-50 Years, Consumer or other non health professional	Humira® (adalimumab) Crohn's disease	Tioguanine	Tiredness, Itching all over, Itchy rash, Rash erythematous, Absence of menstruation	Unknown
6	NL-ABBVIE-18K-114-2295085-00, female, 40-50 years, Consumer or other non health professional	Humira® (adalimumab) 40 milligram / 1 Months Ulcerative colitis	Azithromycin	Tiredness, Nausea, Low back pain, Itch, Nosebleed, Scab, Wound healing disturbance of, Inflammation of wound, Stomach pain, Bleeding menstrual heavy, Depressed mood	Dose Not Changed Not Recovered
7	NL-ABBVIE-18K-114-2418893-00, female, 40-50 years, Consumer or other non health professional	Humira® (adalimumab) 40 milligram / 2 Weeks Crohn's disease	Allopurinol Azathioprine	Nausea, Absence of menstruation	Dose Not Changed Not Recovered
8	NL-ABBVIE-18K-114-2561113-00, female, 40-50 years, Consumer or other non health professional	Humira® (adalimumab) 40 milligram / 2 Weeks Psoriatic arthritis		Flu like symptoms, Common cold, Menstrual disorder	Dose Not Changed Not Recovered
9	NL-ABBVIE-17K-114-2195347-00, female, 50-60 years, Consumer or other non health professional	Humira® (adalimumab) Cortisol 40 milligram / 2 Weeks Rheumatoid arthritis Crohn's disease	Hydroxychloroquine Amitriptyline hydrochloride	Urinary infection, Crohn's disease, Recurrent urinary tract infection, Cyst ovary, Ovulation bleeding (PT =metrorrhagia), Scar, Abdominal disorder, Bladder inflammation, Skin warm, Stiffness joints, Joint pain, Wound infection fungal, Common cold, Painful feet, Middle ear infection, Lack of drug effect, Middle ear inflammation, Painful rash, Erythematous rash	- 206 days Drug Withdrawn, Recovered

10	NL-ABBVIE-19K-114-2957188-00, female, 40-50 years, Consumer or other non health professional	Humira® (adalimumab) 40 milligram / 2 Weeks Crohn's disease		Absence of menstruation	1 Days Dose Not Changed Not Recovered
11	NL-ABBVIE-19K-114-3207956-00, female, 20-30 years, Consumer or other non health professional	Humira® (adalimumab) 40 milligram / 2 Weeks Ankylosing spondylitis		Prolonged menses, Coughing	Dose Not Changed Not Recovered
12	NL-LRB-00423813, female, 30-40 Years, Physician	Amgevita® (adalimumab) 1 dosage form / 2 Weeks Colitis ulcerative	Levocetirizine Budesonide Ethinylestradiol/ Levonorgestrel Verapamil Telmisartan Beclometason	Irregular menstruation, Bleeding menstrual heavy	Dose Not Changed Not Recovered, Not Recovered

Dutch Biologic Monitor untill (31-12-2020)

No	**ID, sex, age, primary source**	**Drug, dose, Indication**	**Reported ADRs (PT)**	**Latency after start Action taken Outcome**
13	2180CAB0-7FE9-4A4A-AA34-1321854576FE, female, 30-40 years, patient	Humira® (adalimumab) Artritis psoriatica, Ziekte van Bechterew / Axiale SpA Dose: the second dose was postponed with a week.	Influenza like illness Injection site erythema Menorrhagia Dysmenorrhoea *Menstruation and menstruation pain (abdominal) are heaviest on the first day. Last time I did not recognize this as an adverse event, but now it is striking. I also have more pimples around my period.* *Burden is low, only a little on the first day of the period.*	9 days 9 days Not Recovered

Included reports involved women between 10-20 and 50-60 years old indicated with rheumatoid arthritis (2 cases), psoriatic arthritis (2 cases), ankylosing spondylitis (1 case) and combined axial spondylarthritis *and* psoriatic arthritis (1 case), Crohn's disease (4 cases) or ulcerative colitis (2 cases). Corticosteroid use could be a confounding factor in the association of adalimumab with menstruation cycle disorders [15, 18]. Considering the many reports on rheumatic indications for which corticosteroids are often prescribed, the use of corticosteroids may be underreported.

From the 13 reports Lareb received, 6 reports were on heavy menstrual bleeding (PT menorrhagia: cases 1, 2, 4, 6, 12 and 13) of which two cases also received methotrexate and naproxen (case 1 and 4). One woman reported the use of ethinylestradiol/levonorgestrel (case 12). Furthermore, Lareb received 4 reports on the absence of bleeding periods (PT amenorrhoea: case 4, 5, 7, 10), which may be confounded by the menopause, as these women were all between 40 and 50 years old. Also, IBD has been associated with changes in menstrual pain and its duration [19]. From the reports received by Lareb, 7 reporters suffered from IBD (cases 5, 6, 7, 9, 10 and 12). In these cases, absence of menstruation (PT amenorrhoea) was reported 3 times (case 5, 7, 10) and heavy menstrual bleeding was mentioned twice (case 6 and 12). Case 9 is slightly different from the other reports as the female is older than the rest and beside the metrorrhagia she suffers from an ovarian cyst. Only 4 cases: 2, 3, 11 and 13 were not confounded by indication, comedication or age.

Other sources of information

SmpC:

Menstrual cycle disorders or other uterine bleeding disorders are not mentioned in the Dutch SmPC of adalimumab. However, the US SmPC mentions "*menstrual disorders*" without further specifications, for adalimumab as Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies [20]. Also in the Dutch SmPC of two other TNF-α inhibitors with the same mechanism of action (etanercept and infliximab), this is not described. However, *"menstrual cycle disorders and uterine bleeding disorders (including amenorrhoea)"* is mentioned *sometimes* (≥1/1.000, <1/100), in the Dutch SmPC of the TNF-α inhibitors certolizumab pegol (Cimzia®) and *"menstrual cycle disorders"* is mentioned *sometimes* (≥1/1.000, <1/100) in the Dutch SmPC of golimumab (Simponi®) as an adverse reaction.

Literature

One case report was described by Scheinfeld et al. [21]. A 32-year-old morbidly obese white woman used 40 mg of adalimumab every other week for four months for the indications psoriatic arthritis, psoriasis vulgaris and inverse psoriasis. She developed menorrhagia and severe menstrual pain. She was treated with levonorgestrel and ethinyl estradiol tablets (Aviane®), which resolved some of her menstrual symptoms. Symptoms resolved upon discontinuation of adalimumab.

Two other case reports were described by Bes et al. [22]. A 41-year-old female with ankylosing spondylitis (for 12 years), received subcutaneous adalimumab (40 mg every other week for 6 months). She experienced uterine bleeding 3 days after the 11th adalimumab injection. Until then, she had had regular menstrual cycles lasting for 5 days. This time she had an excessive vaginal bleeding that persisted for 10 days. Curettage was performed and a biopsy was taken, which revealed no findings of malignancy. The excessive bleeding leaded to hemoglobin level reduction to 5 mmol/l for which she was transfused with erythrocyte suspension. After the curettage, the uterine bleeding stopped for 5 days, after which it restarted. She was treated with norethisterone. Patient's bleeding ceased 3 days after therapy and she experienced normal menstrual cycle for 3 months.

A 31-year-old female with ankylosing spondylitis (for 5 years) received subcutaneous adalimumab (40 mg every other week for 4 months) [22]. Her regular menstrual cycle lasted 6 days. After the 8th dose of adalimumab she experienced prolonged menstrual bleeding (11 days). Her bleeding ceased 3 to 4 days after treatment with an estradiol-containing preparation and an oral iron preparation was commenced because of a 0.7 g/dl decrease in hemoglobin. Adalimumab was stopped. After this she experienced normal menstrual cycles.

Other databases

Because of numerous confounding factors in the reports received by Lareb, additional reports were included from the Eudravigilance database. This database contained 602 reports on menstrual cycle and uterine bleeding disorders as listed in Table 4. Five reports that were not confounded by age or IBD indication were more extensively investigated and are shown in Table 3. These 5 reports include reports on females from 20 to 37 years old. In all 5 cases the patient recovered from the adverse events after discontinuation and in one case reactions recurred upon re-administration of the drug (case 4).

Table 3. Examples Eudravigilance reports that were not confounded by indication or age.

No	**EV Safety Report Identifier**	**sex, age, country, primary source**	**Drug, dose, Indication**	**Concomitant medication**	**Reported ADRs (LLT), latency**	**Action taken Outcome**
1	GB-ABBOTT-04P-167-0280417-00	Female, 37 years, not specified, United Kingdom	Adalimumab Rheumatoid arthritis	Aluminum chlorohydroxy allantoinate (Alcloxa), paracetamol	Menorrhagia *patient experienced menorrhagia every time she took Humira®*	Recovering/Resolving When the patient stops Humira pre-filled syringe therapy her periods return to normal. *The patient stops taking Humira therapy when her periods are heavy and she starts to take Humira therapy again when her*

						periods are back to normal. Humira therapy is ongoing
2	DE-ABBOTT-06P-062-0351450-00	Female, 20 years, Germany, Healthcare professional (Physician)	Adalimumab Psoriatic arthritis		Dyspnoea dyspnea on exertion Menorrhagia	Discontinued: Stopped after 3rd injection because of menorrhagia Recovered/Resolved – 01/08/2006 - 1mo) Additional information received 4 months after discontinuation: The menorrhagia was not observed again during the following time
3	GB-MHRA-MIDB-ac3c4507-c87e-47a2-9863-b9a5eb42f3ce	Female	Adalimumab (Amgevita) fortnightly Flares of seropositive rheumatoid arthritis		Patient reported heavy per vaginam (PV) bleeding Menorrhagia *this case was considered serious because specified event was: significant menorrhagia*	resolved after withdrawn
4	GB-MHRA-EYC 00226186	Female, 25 years, United Kingdom, Healthcare professional (Physician)	Adalimumab (Humira) 60d - 40mg - Cutaneous Psoriatic arthropathy		menorrhagia and intermenstrual bleeding	Drug withdrawn Stopped and symptoms abated. Restarted and symptoms recurred.
5	CA-ABBVIE-15K-028-1376773	Female, 36 years, Canada, Non Healthcare professional (Consumer or other Non-Health Professional)	Adalimumab (Humira) 40mg - Subcutaneous Psoriatic arthropathy - Psoriatic Arthritis	Hydromorphone	All of her medical conditions are getting worse Pain in coccyx Because of hernias in back pain goes up to her neck and causes migraines, vomits when had migraines Fibromyalgia, sacroiliitis is causing pain, Urine was dark and having period more frequently/ sometimes could be having period 3 times in 3 weeks	Drug withdrawn She discontinued Humira® in Jan 2015, in case she would need surgery for two hernias in her back and since then, her urine and periods are more normal

Disproportionality analysis

Table 4. ROR for Menstrual cycle and uterine bleeding disorders (HLGT)

	ADR (Meddra PT)	**Number of reports**	**ROR (95% CI)**
Lareb reports	Menorrhagia	6	1.0 (0.4 – 2.2)
	Amenorrhagia	4	0.8 (0.3 – 2.1)
WHO#[23]	Amenorrhoea	167	0.3 (0.2 – 0.3)
	Heavy menstrual bleeding	452	0.6 (0.6 – 0.7)
	Menstrual disorder	191	0.6 (0.5 – 0.7)
	Intermenstrual bleeding	157	0.2 (0.1 – 0.2)
Eudravigilance#[24]	Amenorrhoea	39	0.4 (0.3 – 0.6)
	Dysmenorrhoea	6	0.2 (0.1 – 0.5)
	Heavy menstrual bleeding	53	0.5 (0.4 – 0.7)
	Intermenstrual bleeding	24	0.3 (0.2 – 0.4)
	Menstrual disorder	19	0.5 (0.3 – 0.8)
	Menstruation delayed	7	0.2 (0.1 – 0.5)
	Menstruation irregular	17	0.4 (0.2 – 0.6)
	Oligomenorrhoea	5	1.0 (0.4 – 2.3)

ADR (Meddra PT)	Number of reports	ROR (95% CI)
Polymenorrhoea	5	0.4 (0.2 – 1.0)

The ROR was only calculated on spontaneous reports for ADRs that were reported >3 times. Therefore, Lareb reports on menstrual disorder, menstruation irregular and metrorrhagia were not included in ROR calculations.
#Information extracted on 26-05-2021.

Prescription data

Table 5. Number of patients using adalimumab in the Netherlands between 2016 and 2020 according to the GIP database [25]

Drug	2016	2017	2018	2019	2020
L04AB04 Adalimumab*	19,763	20,679	21,774	25,261	26,742

*Adalimumab was transferred to intramural healthcare as per 01-01-2012. Therefore, the actual number of patients using adalimumab may be higher than reported.

Mechanism

TNF-α levels fluctuate during the menstrual cycle [26]. TNF-α concentrations are significantly increased during the late follicular phase and during the mid-luteal phase, whereas levels are significantly decreased in the early luteal phase [27]. Beside the observation that TNF-α concentrations fluctuate during the menstruation cycle, it has not been elucidated whether TNF- α blockers could influence the menstruation cycle.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb has received 13 reports on menstruation cycle disorders in association with adalimumab use that contain excessive bleeding (menorrhagia) as well as periods without bleeding (amenorrhoea). Taking into account the exposure for adalimumab this is not a highly reported event. Additionally, three case reports describing four patients with severe complaints were found in literature. As described in literature, confounding factors for the association of adalimumab with menstruation cycle disorders are the use of methotrexate or corticosteroids, IBD indication, or higher age (menopause). As the majority of the reports received by Lareb were confounded, 5 reports from the Eudravigilance database on menstrual cycle disorders and adalimumab that were not confounded by age, comedication or indication (IBD) were included in this report. For adalimumab menstruation cycle disorders is not mentioned in the Dutch SmPC, although the US FDA SmPC mentions menstrual disorders as Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies. For two other TNF-α inhibitors: certolizumab pegol and golimumab, menstruation disorders are also mentioned in the SmPC. Therefor the association between adalimumab and menstrual disorders should be further investigated.

References

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This signal has been raised on September 23, 2021. 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.cbg-meb.nl