Adalimumab and hypoglycaemia

Introduction

Adalimumab is indicated for *various forms of arthritis (including rheumatoid arthritis), plaque psoriasis, Crohn's disease, ulcerative colitis, hidradenitis and non-infectious uveitis*. It is a human monoclonal antibody which blocks tumour necrosis factor alpha (TNF-α). Adalimumab was granted marketing authorization throughout the European Union in 2003. [1]

Hypoglycaemia is a well know adverse effect of antidiabetic drugs. Also, non-antidiabetic treatments, like betablockers, fluoroquinolones and selective serotonin reuptake inhibitors, can cause hypoglycaemia mainly in patients known with diabetes. Potential mechanisms of drug-induced hypoglycaemia are stimulating insulin release, reducing insulin clearance, interfering with glucose metabolism or potentiating the hypoglycaemic effect of antidiabetic drugs. Many drugs inducing hypoglycaemia may also induce hyperglycaemia [2].
Drug-induced hypoglycaemia is usually mild but may be severe [2]. Early symptoms of hypoglycaemia include shakiness, dizziness, sweating, hunger, palpitations, yawning, restlessness, confusion, headache, tingling in hands, feet or lips, double or blurred vision and mood swings. Severe hypoglycaemia can lead to drowsiness and loss of consciousness and eventually result in a coma [3].

Reports

In the period from June 13th 2007 to May 30th 2022 the Netherlands Pharmacovigilance Centre Lareb received 6 reports of hypoglycaemia or blood glucose decreased with the use of adalimumab [4].

Table 1. Reports of hypoglycaemia (PT) and blood glucose decreased (PT) in association with adalimumab in the Lareb database [4]

No	WWUCID, sex, age, primary source	Drug (S/IA), Dosage, Indication	Concomitant medication	Reported ADRs	Latency after start, Action taken, Outcome
1	NL-LRB-65958, F, 60-70 Years, Other health professional	Adalimumab, 40 mg/2 weeks, Rheumatoid arthritis (IA) ---------- Insulin aspart, 48 IU/1 day, Diabetes mellitus insulin dependent (IA) ---------- Insulin glargine, 36 IU/1 day, Diabetes mellitus insulin dependent (IA)	Fluticasone inhalation powder, Timolol/dorzolamide eye drops Carmellose eyedrops, Povidon/Polyvinylalcohol eye drops, Methotrexate, Diclofenac, Folic acid, Alendronic acid, Atenolol/Chloortalidone, Levothyroxine, Omeprazole, Metoclopramide, Carbasalate calcium	Hypoglycaemia, Drug interaction	5 Months, Adalimumab – dose not changed Insuline aspart – dose reduced Insuline glargine – dose reduced, Recovered
2	NL-LRB-86756, M, 50-60 Years, Physician	Adalimumab, 40 mg/?, Psoriatic arthritis		Hypoglycaemia	2 Months, Drug withdrawn, Recovered
3	NL-ABBVIE-19K-114-2758034-00, ?, 60-70 years, Other health professional	Adalimumab, -, Rheumatoid arthritis		Hypoglycemic episode	-, Unknown, Unknown
4	NL-ABBVIE-21K-114-4135250-00, F, 40-50 Years, Consumer or other non health professional	Adalimumab, ?/2 weeks, Behcet's syndrome	Dexamethasone, Insulin normal	Hypoglycemia, Headache, Corneal inflammation, Off label use	-, Dose not changed, Recovering -, Dose not changed, Recovered -, Dose not changed, Not recovered

No	WWUCID, sex, age, primary source	Drug (S/IA), Dosage, Indication	Concomitant medication	Reported ADRs	Latency after start, Action taken, Outcome
5	NL-LRB-00710299, F, 40-50 Years, Consumer or other non health professional	Adalimumab, 1 dosage form/2 weeks, Behcet's disease	Insulin aspart, Insulin glargine	Hypoglycaemia	3 Days, Drug withdrawn, Recovering
6	NL-ABBVIE-20K-114-3484427-00, F, 50-60 years, Consumer or other non health professional	Adalimumab, 40 mg/2 weeks, Rheumatoid arthritis	Prednisone	Serum glucose decreased, Blood pressure low Dizzy spells	-, Dose not changed, Unknown -, Dose not changed, Recovered

Patient 1, 4 and 5 are known with type 1 diabetes mellitus. Patient 2 is known with an unknown type of diabetes mellitus. For patient 3 and 6 it is unknown if they have diabetes mellitus in their medical history. Patient 1 and 5 were hospitalised due to hypoglycaemia and received a glucose infusion as treatment.

Other sources of information

Summary of Product Characteristics (SmPC)

Hypoglycaemia is not mentioned in the SmPCs of adalimumab of various brands, but hyperglycaemia is labeled as an adverse reaction in section 4.8 [1, 5-10].

Literature

Boulton et al describe the case of a 55-year-old female with stable type 1 diabetes and rheumatoid arthritis who developed severe hypoglycaemia within 12 hours after the first administration of adalimumab for rheumatoid arthritis. Hypoglycaemia recurred 24 hours later and the patient recovered after withdrawal of adalimumab. This patient had also developed two severe hypoglycaemic attacks after starting etanercept for rheumatoid arthritis one year earlier [11]. Czajkowska et al published a case series regarding nine non-diabetic patients who developed hypoglycaemia with one or multiple TNF-α inhibitors, e.g. adalimumab (4), infliximab (6), etanercept (1), certolizumab (2) and golimumab (1) [12]

Mechanism

Adalimumab and other TNF-α inhibitors can play a role in glycaemic control, since TNF-α has been associated with glucose homeostasis. TNF-α appears to block insulin-mediated uptake of glucose in adipose tissue by down-regulation of glucose transporter mechanisms. This can lead to increased insulin resistance. TNF-α inhibitors can block this action leading to an increased insulin sensitivity and resulting in hypoglycaemia in patients with and without a known history of diabetes [11-13].

Class effect

In the SmPC of etanercept, also a TNF-α inhibitor, a warning is included regarding hypoglycaemia in patients treated for diabetes: “There have been reports of hypoglycaemia following initiation of etanercept (Enbrel) in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients” [14].

In literature various case reports regarding TNF-α inhibitor induced hypoglycaemia in patients have been published, namely three cases of etanercept in a patient with type 2 diabetes [13, 15, 16], one case of infliximab in a patient with type 2 diabetes [17] and one case of infliximab in a non-diabetic patient [18]. Also, insulin metabolism has been studied in non-diabetic patients with rheumatoid arthritis being treated with infliximab. Both shortly (2 hours) and more long-term (6 and 14 weeks) after administration of administration of infliximab an improved insulin sensitivity and reduced insulin resistance were noted [19]. This is in contrast to a study in non-diabetic patients with juvenile idiopathic arthritis, ankylosing spondylitis and psoriatic arthritis where during the first six months of treatment with adalimumab, infliximab of etanercept no influence on glucose metabolism was noticed [20].

Databases

Table 2. Reports of hypoglycaemia (PT) and blood glucose decreased (PT) with adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab in the Lareb [4], WHO [21] and Eudravigilance database [22]

Database	Drug	Preferred terms	Number of reports	ROR (95% CI)
Lareb	Adalimumab	Hypoglycaemia	5	0.78 (0.32-1.88)
		Blood glucose decreased	1	-
	Etanercept	Hypoglycaemia	3	0.88 (0.28-2.73)
		Blood glucose decreased	0	-
	Infliximab	Hypoglycaemia	2	-
		Blood glucose decreased	0	-
WHO	Adalimumab	Hypoglycaemia	184	0.11 (0.09-0.12)
		Blood glucose decreased	442	0.51 (0.46-0.56)
	Certolizumab pegol	Hypoglycaemia	15	0.09 (0.05-0.15)
		Blood glucose decreased	25	0.30 (0.20-0.44)
	Etanercept	Hypoglycaemia	163	0.10 (0.09-0.12)
		Blood glucose decreased	314	0.40 (0.36-0.45)
	Golimumab	Hypoglycaemia	10	0.09 (0.05-0.16)
		Blood glucose decreased	6	0.10 (0.05-0.22)
	Infliximab	Hypoglycaemia	96	0.19 (0.16-0.23)
		Blood glucose decreased	74	0.29 (0.23-0.37)
Eudravigilance	Adalimumab	Hypoglycaemia	61	0.16 (0.13-0.21)
		Blood glucose decreased	48	0.39 (0.30-0.52)
	Certolizumab pegol	Hypoglycaemia	11	0.11 (0.06-0.21)
		Blood glucose decreased	4	0.13 (0.05-0.34)
	Etanercept	Hypoglycaemia	120	0.10 (0.08-0.12)
		Blood glucose decreased	154	0.40 (0.34-0.47)
	Golimumab	Hypoglycaemia	6	0.06 (0.03-0.14)
		Blood glucose decreased	1	0.03 (0.00-0.23)
	Infliximab	Hypoglycaemia	93	0.19 (0.16-0.24)
		Blood glucose decreased	43	0.28 (0.20-0.37)

Prescription data

Table 3. Number of patients using adalimumab in the Netherlands between 2017 and 2021 [23]

Drug	2017	2018	2019	2020	2021
Adalimumab	20,679	21,774	25,502	28,177	29,954

Discussion and conclusion

Lareb received 6 reports of hypoglycaemia or decreased blood glucose associated with the use of adalimumab, among which 4 patients known with diabetes. Confounding by other factors that could affect glucose levels and insulin requirement such as concomitant drugs (e.g. antidiabetics and betablockers), disease activity or concurrent infections, could not be excluded in all reports, since the extent of documentation varied. However, the improvement of glucose levels after dose reduction of insulin or discontinuation of adalimumab in three reports suggest that adalimumab may induce hypoglycaemia. Hypoglycaemia is not described in the Dutch SmPC of adalimumab, but is in the SmPC of another TNF-α inhibitor etanercept. Multiple case reports of hypoglycaemia after treatment with various TNF-α inhibitors have been described in literature including a plausible mechanism. Since hypoglycaemia can have severe consequences, attention for this adverse reaction is warranted.

References

1. Dutch SmPC Humira [updated 14-09-202123-03-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_nl.pdf.
2. Ben Salem C, Fathallah N, Hmouda H, Bouraoui K. Drug-induced hypoglycaemia: an update. Drug Saf. 2011;34(1):21-45.
3. MayoClinic. Hypoglycemia [updated 04-05-2022. Available from: https://www.mayoclinic.org/diseases-conditions/hypoglycemia/symptoms-causes/syc-20373685.
4. Netherlands Pharmacovigilance Centre Lareb Database [Internet]. [cited 31-05-2022].
5. Dutch SmPC Amgevita [updated 17-12-202114-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/amgevita-epar-product-information_nl.pdf.
6. Dutch SmPC Hyrimoz [updated 03-03-202214-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/hyrimoz-epar-product-information_nl.pdf.
7. Dutch SmPC Yuflyma [updated 11-03-202214-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/yuflyma-epar-product-information_en.pdf.
8. Dutch SmPC Hulio [updated 12-01-202214-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/hulio-epar-product-information_en.pdf.
9. Dutch SmPC Idacio [updated 01-03-202214-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/idacio-epar-product-information_en.pdf.
10. Dutch SmPC Imraldi [updated 07-06-202214-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/imraldi-epar-product-information_en.pdf.
11. Boulton JG, Bourne JT. Unstable diabetes in a patient receiving anti-TNF-alpha for rheumatoid arthritis. Rheumatology (Oxford). 2007;46(1):178-9.
12. Czajkowska JB, Shutty B, Zito S. Development of low blood glucose readings in nine non-diabetic patients treated with tumor necrosis factor-alpha inhibitors: a case series. J Med Case Rep. 2012;6:5.
13. Wambier CG, Foss-Freitas MC, Paschoal RS, Tomazini MV, Simao JC, Foss MC, et al. Severe hypoglycemia after initiation of anti-tumor necrosis factor therapy with etanercept in a patient with generalized pustular psoriasis and type 2 diabetes mellitus. J Am Acad Dermatol. 2009;60(5):883-5.
14. Dutch SmPC Enbrel [updated 29-04-202214-06-2022]. Available from: https://www.ema.europa.eu/en/documents/product-information/enbrel-epar-product-information_nl.pdf.
15. Farrokhi F, Taylor HC, McBride NM. Etanercept-induced hypoglycemia and improved glycemic control in a patient with type 2 diabetes. Endocr Pract. 2011;17(2):306-7.
16. Cheung D, Bryer-Ash M. Persistent hypoglycemia in a patient with diabetes taking etanercept for the treatment of psoriasis. J Am Acad Dermatol. 2009;60(6):1032-6.
17. Mah JY, Teng J, Gilfillan C. Tumour necrosis factor-alpha inhibitor induced recurrent symptomatic hypoglycaemia. Intern Med J. 2019;49(11):1460-1.
18. Zabalza L, de Carlos J, Ezcurra I, Rullan M, Elosua A, Rubio S, et al. Infliximab-induced hypoglycemia, a rare but relevant side effect. Rev Esp Enferm Dig. 2022;114(6):364-5.
19. Solomon DH, Massarotti E, Garg R, Liu J, Canning C, Schneeweiss S. Association between disease-modifying antirheumatic drugs and diabetes risk in patients with rheumatoid arthritis and psoriasis. JAMA. 2011;305(24):2525-31.
20. da Silva BS, Bonfa E, de Moraes JC, Saad CG, Ribeiro AC, Goncalves CR, et al. Effects of anti-TNF therapy on glucose metabolism in patients with ankylosing spondylitis, psoriatic arthritis or juvenile idiopathic arthritis. Biologicals. 2010;38(5):567-9.
21. WHO Vigibase [Internet]. [cited 31-05-2022]. Available from: https://vigilyze.who-umc.org/ (acces restricted).
22. Eudravigilance [Internet]. [cited 31-05-2022]. Available from: http://bi.eudra.org (access restricted).
23. GIP Database - Drug Information System of the Dutch Health Care Insurance Board [Internet]. [cited 31-05-2022]. Available from: https://www.gipdatabank.nl/databank?infotype=g&label=00-totaal&tabel_g_00-totaal=R_04_addon&geg=gebr&item=b-Biologicals.

This signal has been raised on September 15, 2022. 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