



Refractoriness to drugs in migraine may be the result of developing anti-drug antibodies

K. Maselis^{a,*}, R. Žekevičiūtė^a, A. Vaitkus^b

^a Hospital of Lithuanian, University of Health Sciences Kauno klinikos, Eivenių g. 2, Kaunas, Lithuania

^b Lithuanian University of Health Sciences, Eivenių g. 2, Kaunas, Lithuania

ARTICLE INFO

Keywords:

Refractory migraine
Anti-drug antibody
Pathophysiology
Immunology

ABSTRACT

Introduction: Migraine is a common neurological disease and is listed second among the most disabling health conditions worldwide. Refractory migraine (RM) is a term used to emphasize the unresponsiveness of migraine to various treatment options, encompassing both episodic refractory and chronic refractory migraine. In this paper we discuss various known and possible mechanisms of pharmacological refractoriness in RM, such as possible involvement of the gut microbiome, the blood-brain barrier, migraine genetics and various mechanisms of pharmacokinetic and pharmacodynamic tolerance. Development of medication-overuse headache as a secondary disorder following migraine is also considered. We argue that the available literature is insufficient to fully explain the mechanisms of refractoriness and we present our hypothesis.

HYPOTHESIS: Refractoriness to drugs in migraine may be the result of developing anti-drug antibodies. Most migraine drugs are small molecules, which cannot elicit an immune response on their own due to their size. However, such molecules can bind to peptide carriers in their vicinity, greatly increasing their immunogenicity. A small molecule possessing this binding ability is called a hapten. Haptens form hapten-carrier complexes (HCCs), which can evoke powerful immune responses. Immune reactions to HCCs are known to be predominantly 'drug allergies' or type 1 drug hypersensitivity reactions', usually resulting from IgE or non-IgE mediated mast cell degranulation. We argue that the immune reaction to HCCs can take shape in developing neutralizing anti-drug antibodies (ADA) in the form of IgG and IgA class antibodies. Since biological therapeutics, such as various monoclonal antibodies, face the issue of ADA-induced drug tolerance, HCCs, being similar in the sense that they carry peptide antigens, are of sufficient size and may be considerably immunogenic, can be responded to in a similar way by producing neutralizing ADA. Furthermore, we argue that such responses are expected to happen more frequently than is thought, due to IgG and IgA being prevalent antibodies, which utilize their neutralizing capabilities on regular basis. Finally, it is important to consider that neutralization reactions in normal immune responses are typically asymptomatic, with the only clinical expression being progressive drug tolerance. These cases may be overshadowed by the life-threatening cases of drug allergy induced anaphylaxis, possibly leading to neutralization reactions being underrecognized.

Discussion: This hypothesis aims to stimulate more research regarding drug resistance, and if it receives support from empirical evidence, it may help further elucidate the mechanisms underlying refractory diseases and contribute to the development of more effective treatment of many disorders.

Background

Drug resistance (DR) is a prevailing issue in treatment of various diseases. Among are neurological diseases, such as migraine, psychiatric disorders, arterial hypertension, gastrointestinal disorders and many other conditions that may be resistant to pharmacotherapy. Different medications have different underlying mechanisms of DR that are in

play, therefore each drug class must be examined individually to make valid claims regarding the pathophysiological factors of developing resistance. To examine every case of drug resistance of various diseases would be beyond the scope of this article, therefore the authors have chosen to use DR in migraine treatment as an example to present the hypothesis. However, the ideas of the hypothesis in their essence are not restricted exclusively to migraine treatment and may be considered in

* Corresponding author.

E-mail address: kipras.maselis@gmail.com (K. Maselis).

<https://doi.org/10.1016/j.mehy.2020.110459>

Received 26 October 2020; Received in revised form 9 December 2020; Accepted 11 December 2020

Available online 15 December 2020

0306-9877/© 2020 Elsevier Ltd. All rights reserved.

other drug-resistant diseases.

Introduction

Migraine is a common neurological disease, and is listed second among the most disabling health conditions worldwide [1]. Migraine can greatly impact persons' quality of life and is responsible for considerable economic costs [2]. Epidemiological studies estimate the prevalence of migraine to be around 12% in total population. However, a study by Yeh et al. found the prevalence in neurologists to be up to 3-fold that of general population, pointing to possible underrecognition of the disease in non-specialists [3].

Chronic migraine (CM) is characterized by a migraine headache, which occurs 15 or more days per month for 3 consecutive months, and is associated with patient's greater functional impairment. Prevalence of the condition is estimated to be around 1–2% of global population, and around 2.5% of episodic migraine cases progress into chronic migraine [4].

The condition develops as episodic migraine undergoes gradual transformation over time [5]. However, it is not solely the frequency of headache attacks that changes. It has been revealed that significant pathophysiological changes in chronic migraine are responsible for the development of the condition, such as alterations of top-down pain modulation, trigeminal sensitization, and biochemical changes in the brain [6]. Furthermore, as opposed to episodic migraine sufferers, more comorbidities are often present in chronic migraine patients, such as gastrointestinal disorders, psychiatric disorders, and cardiovascular disorders, suggesting that the disease may have deeper pathophysiological roots than episodic migraine [4,7,8].

In contrast to episodic migraine, chronic migraine poses greater diagnostic and treatment challenges. From a diagnostic standpoint, it can be difficult to distinguish it from medication-overuse headache, which is a secondary headache disorder and develops as a result of chronic analgesic medication use, often from use of triptans or opioids. From a treatment standpoint, treatment options are often eventually exhausted due to chronic migraine often becoming resistant to numerous different medications [9].

Refractory migraine (RM) is a term used to emphasize the unresponsiveness of migraine to various treatment options. As pointed out in a recent review, there is a lack of consensus regarding the definition of RM, such as disagreements related to headache diagnosis, headache-related disability, type of and number of medications failed in attempts to control the condition [10]. Such disagreements about the definitions and criteria present difficulties for the scientific community to collect and systemize data regarding RM, which is reflected in the current literature as a lack of a consistent body of evidence.

In this paper, we use the term 'refractory migraine' to refer to both episodic refractory migraine and chronic refractory migraine, focusing solely on the refractoriness as unresponsiveness to a number of different drug classes as the primary feature of RM. Accurate definitions of RM for the presentation of the hypothesis, however, are not necessary.

Mechanisms of refractoriness

Failure to reach the desired pharmacological response can manifest from a variety of sources. Drug resistance in migraine has to be briefly reviewed in light of available literature to assess whether known mechanisms of refractoriness have sufficient explanatory power for this phenomenon. Therefore, several known and possible causes of drug resistance in migraine are discussed.

Gut and pharmacokinetics

Since many drugs are taken orally, the gut may play a vital role in drug kinetics, for if the concentration of the drug cannot reach a sufficient level in the bloodstream, it cannot systemically exert its intended

effects. Following this logic, malabsorption syndromes may be hypothesized to have considerable negative effects on drug absorption, since available surface area of GI decreases substantially. This idea was examined in a number of studies. For instance, patients following bariatric surgery for obesity have reduced functional GI surface area, however, reports demonstrate that in such patients medication bioavailability varies by drug type, and while in some cases a decrease was observed, in many cases drug concentration remained unaffected or even increased after surgery, possibly due to a higher proportion of drugs surviving by having less contact with GI enzymes [11,12].

The gut microbiome has been found to have substantial influence over drug kinetics, having effects on absorption, pro-drug activation, or drug inactivation, and metabolism. NSAIDs, which are common in acute treatment of migraine, are metabolized by gut bacteria, however, the possible net effect of this process in this case is increased toxicity to the gut, not decreased systemic activity [13]. From this perspective, therefore, it is unlikely that bacterial metabolism is responsible for cases of NSAID resistance for in migraine patients. In a similar manner, gut microbiome has been proposed to have effects on metabolism of anti-hypertensive medication, although the evidence of such interaction appears to be mainly on a theoretical level [14,15]. If suggested concepts become backed by more empirical evidence, resistance to beta-adrenoceptor antagonists, which are used as prophylactic agents in migraine, could be examined through this lens.

Mechanisms of tolerance to migraine medication

Tolerance can be defined as reduction of drug efficacy due to its repeated administration. A study on migraine prophylactic drug tolerance has observed several viable mechanisms of action [16]. Besides pharmacological tolerance, behavioral and cross-tolerance need to be considered when identifying the cause for refractoriness. However, the literature regarding these mechanisms is scarce, and no substantial evidence is readily available.

Opioids are among the most potent analgesics and are used to treat acute pain in migraine. Several mechanisms of developing pharmacological tolerance exist, primarily involving mu-receptor endocytosis and desensitization to opioid agents [17]. Another noteworthy mechanism involving opioid medication is that of gut-brain interaction. It has been demonstrated that alterations in gut microbiome take place as a result of chronic opioid exposure and these changes may lead to development of pharmacological resistance to analgesic effects [18]. With this in mind, opioids present a high risk of developing tolerance, which can be appreciated in the context of ongoing opioid crisis.

Another mechanism of possible pharmacological migraine drug tolerance is related to the function of the blood-brain barrier (BBB). Inflammatory responses, such as that during exposure to chronic pain, elicit a cascade of molecular and cellular responses in the brain. Such responses increase the permeability of BBB, leading to higher concentrations of CGRP (Calcitonin-gene related peptide), substance P and other inflammatory molecules [19]. Inflammatory pain also causes an increase in expression of P-glycoprotein, which functions as a powerful drug efflux pump in the BBB. As a result, P-glycoprotein may in some cases be an obstacle for drugs to reach CNS to exert their effects, leading to a decrease in drug efficacy.

However, development of drug tolerance may have a broader pathophysiological background. In *Drosophila melanogaster*, it has been shown that even a single exposure to a sedative creates epigenetic effects which ultimately result in changes in the excitability of neurons in the brain [20]. Upon exposure to a sedative, the *slo* gene, which is responsible for the coding of the Ca²⁺ dependent K⁺ channels in the neuron membrane, was shown to be upregulated, resulting in upregulation ion channels. Further exposure to the drug led to significant and consistent tolerance. Whether this mechanism is applicable to humans remains unclear.

Apparent tolerance to analgesic drugs may actually be a consequence

of chronic drug overuse, causing medication-overuse headache, which is classified as a secondary headache condition [9]. The condition develops in patients, who typically suffer from a primary headache condition, such as migraine, and who have commonly and consistently used analgesic drugs for pain management. Therefore, perceived decreases in efficacy of analgesic drugs may erroneously be attributed to drug tolerance.

Genetics in migraine

It has been generally established that migraine may have a genetic component [21]. This concept has been backed by discovery of familial hemiplegic migraine (FHM) and other specific disorders, such as episodic ataxia 2 and spinocerebellar ataxia type 6, which have been shown to be hereditary [22]. A mounting body of evidence regarding identification of various genetic nucleotide polymorphisms has been accumulating since.

Migraine has been referred to as being polygenic. Different polymorphisms have been associated with different pathophysiological links [22]. Considering the spectrum of pathophysiological factors in migraine, it comes as no surprise that refractory cases persistently develop, as currently available drugs are limited in their areas of effect.

Genetic influence may present itself not only through intricacies and variations of migraine pathophysiology, but also as drug resistance. Specific single nucleotide mutations have been associated with decreased efficacy of triptans and ergotamine in treating acute migraine attacks, suggesting that heterogeneity of migraine genetics may be relevant to the individualized selection of potential agents for treatment [23]. This notion is also supported by emerging evidence of individual genetic polymorphisms affecting drug metabolism through CYP450 enzyme systems [24]. Consequently, metabolic variations may affect drug bioavailability and drug efficacy.

Context for the hypothesis

Although many theories are possible to underlie the refractoriness in migraine, many of them have limited support in the available literature. We argue that the current evidence to explain the causes of refractory migraine is insufficient. Regarding this matter, we present our hypothesis.

The hypothesis

Refractoriness to drugs in migraine may be the result of developing anti-drug antibodies.

Supporting evidence

The issue of anti-drug antibodies

Anti-drug antibodies (ADA) are recognized as a problem for biological therapy. Anti-tumor-necrosis-factor (anti-TNF) agents adalimumab and infliximab, anti-CD20 agent rituximab and many others are studied in vivo in attempts to detect possible ADA [25–27]. Such efforts are grounded in the fact that biological agents are protein-based, and being so, they may have immense immunogenic potential, evoking an immune-mediated response from the host [28]. Ultimately the result may be neutralization of the agent by formation of immune complexes following ADA development. However, it has been demonstrated that ADA development is not necessarily associated with decreased drug efficacy [29,30]. Hence, generation of ADA does not implicitly mean drug resistance.

Substantial progress has been made in the development of ADA assay methods [31–34]. However, assessment of ADAs in the literature is not usually carried out by analysis of different immunoglobulin classes. But since neutralization mechanisms typically happen through IgG or IgA

class antibodies, we presume IgG/IgA are responsible for the majority of the ADA, as found in some studies [35–37].

As explained above, ADA is considered as a cause of drug resistance in biological therapy. Here, however, we argue that traditional non-biological drugs, such as NSAIDs, triptans and other analgetics used for migraine, may be subject to ADA formation as well.

Eliciting a humoral immune response

In order to support the claim of the hypothesis, we must first review how the specific humoral immune response against foreign antigens develops.

Antibody production is the result of B cell activation. Once activated, the specific B cell will clone itself and terminally differentiate into an antibody producing plasma cell [38].

Activation of a B cell takes place in the process of antigen presentation. A mature B cell is a professional antigen presenting cell (APC) and is able to sample the environment through direct binding of a molecule to a B cell receptor (BCR) [39]. Once a foreign antigen is bound to a BCR, it is endocytosed and the content is decomposed. Afterwards, the antigen undergoes a process of attachment to the major histocompatibility complex class 2 protein (pMHC II) and the antigen-pMHC II conjugate is transported to the surface of the cell to be presented on the outer membrane of the B cell, along with expression of other costimulatory molecules [40]. When the antigen-pMHC II conjugate possessing B cell and a CD4+ T cell come into contact, B cell activation can take place and antibody formation events are set into motion [39].

Not all antigens can be presented on the pMHC II. Antigen has to be sufficient in size, otherwise it is too small to bind [41]. The pMHC II usually binds molecules at least of the size of a small peptide, therefore, non-biological drugs, including most drugs for migraine, fit the category of small size and, since they cannot launch a response cascade through antigen presentation, are unable to elicit an immune response on their own, i.e. are not immunogenic.

However, it is known that these small molecules through the course of absorption into the bloodstream can sometimes bind to small peptides in their vicinity, and the new conjugate structurally develops different antigenic properties, often greatly amplifying immunogenicity as well [42]. Molecules, which become immunogenic with this peptide-binding ability are known as haptens in the context of immunology and have been deeply studied since their discovery of Karl Landsteiner in the early 20th century [43]. Haptens, when bound to a peptide, form a hapten-carrier complex (HCC) and can evoke powerful immune reactions [44]. Hence, further discussion of small drug molecule immunogenicity must be conducted through recognition of (1) drugs being haptens and (2) immune responses to HCCs.

Drugs as haptens

A wide spectrum of molecules are now recognized as haptens. For instance, HaptenDB is a free and easily accessible database of haptens, featuring over a thousand haptens, including morphine and several other studied drugs [45]. The fact that many drugs may be haptens is also proved by a wide array of medications causing anaphylactic reactions, since such reactions are typically a result of HCC formation [44,46]. Common drugs in that regard include NSAIDs, beta-lactam antibiotics and radiocontrast media. Therefore, many more drugs in migraine, and in other diseases for that matter, may be considered as haptens.

Typical immune reactions to HCCs

Immune responses to HCCs are typically described as IgE-mediated type 1 drug hypersensitivity reactions in the literature. Along with other mechanisms, they feature mast cell degranulation, with release of potent immune mediators, causing life-threatening conditions, involving

acute cardiovascular, respiratory, gastrointestinal and skin manifestations [44]. However, a considerable part of type 1 hypersensitivity reactions are non-IgE mediated, in which other cofactors and mediators, such as complement activation, IgG-related mast cell degranulation, and kalikrein activation systems, are in play [47]. Still, both IgE and non-IgE mediated reactions lead to what is described as “drug hypersensitivity”, featuring strong allergic reactions or even anaphylaxis.

Proposed immune reactions to HCCs

HCCs are similar to biological drugs we have described in this paper in the sense that both types of compounds can feature similar peptidic antigens, considerable antigen size and immunogenicity. If such similarities are considered, one could argue, that the immune system can occasionally respond to HCCs in the same way it responds to biological agents – by regarding the HCC molecules as foreign and subsequently producing ADA. As already described, ADA may often manifest as IgG and IgA, which neutralize the antigen in the formation of immune complexes (ICs). In light of the fact that IgG is the most common antibody and that neutralizing function is a crucial function of this antibody class, such responses are to be expected [48]. In the case of neutralization of HCCs, immune complexes would then be cleared by the innate immune system by the means of phagocytosis, diminishing the intended magnitude of effect of the administered drug, without any allergic reaction.

Silent reactions and hypersensitivity

Immune complex formation does not predict host reaction on a macroscopic scale. For instance, in viral diseases, antibody-dependent neutralization is a vital part of host defense, resulting in immune complex formation. But in the case of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there has been astounding heterogeneity in disease severity [49]. While some patients are asymptomatic, in others immune complex formation leads to type 3 hypersensitivity reactions, such as vasculitis [50]. Such cases demonstrate, that while the immune system of each host is responsive to a threat, it does not necessarily predict clinical manifestations.

Even though an example of viral infection might not be the most adequate of scenarios to analyze, for infections can escalate quickly and are an emergency to the immune system, the notion that neutralization reactions may be asymptomatic holds true in the case of ADA against biological therapeutics and in the cases of vaccination, regardless of antigens being recognized, analyzed, and conjugated, following the production of neutralizing antibodies. For these reasons, immune reactions against HCCs may also be asymptomatic on a macroscopic scale.

Finally, perhaps allergic reactions receive the most attention regarding this subject due to them being the most clinically significant as anaphylactic reactions may be life-threatening. Silent ADA drug neutralizing reactions may be underrecognized and manifest only as progressing drug tolerance.

Discussion

Drug resistance is an issue in many diseases and is the reason for great suffering in many patients, including those with migraine. Inability to solve these issues drives costs of treatment and generates frustration in patient and physician alike. Therefore, drug resistance as a subject should be actively studied for possible solutions and the hypothesis aims to stimulate research in this area.

A wide array of causes may underlie drug resistance in different diseases; hence the authors have chosen to present the hypothesis through the lens a single disorder. Moreover, we find that in-depth analysis of possible etiology of refractoriness is essential in a given disorder, for known causes have to be excluded first in order to consider a novel mechanism. Cases of drug resistant disorders may be very

heterogeneous and need to be investigated patiently and thoroughly.

In terms of migraine disorders, we hoped to show that drug resistance mechanisms in refractory migraine are insufficiently explained and that a possible explanation for refractoriness might be development of immunologically mediated drug tolerance by formation of ADA. Should this idea be backed by empirical evidence, the hypothesis could be extrapolated into a general subject of immune-mediated drug resistance, solving of which could prove useful to a variety of different medical fields, not just neurology.

In contradiction to the hypothesis, presence of ADA would possibly lead to slow and progressive reduction in drug efficacy, i.e. drug tolerance. This tolerance would be expected to be drug-specific and to revert back after a period of no drug exposure. However, hard cases of refractory migraine are immediately resistant to multiple drug classes, which is not consistent with the hypothesis. Moreover, as mentioned earlier in the text, even when ADA are present in considerable titers, drug efficacy might not be as affected as thought. Still, considering the number of mechanisms refractory migraine can emerge, immune-mediated responses retain a possibility to explain a fraction of the cases.

Analysis of this subject may become useful not only in attempts to elucidate mechanisms of refractoriness, but also to develop a deeper understanding of how and to what immune responses are generated and carried out, since there are many disorders, such as autoimmune disorders, course of which is yet to be fully controlled.

In order to test the hypothesis, it has to be understood, that ADA as IgA antibodies can also be found in the mucus of various mucous membranes [36]. Therefore, using blood as a sole source of sampling for antibody search may yield inconclusive results and mucus samples may be needed. As the quality of ADA assays improves, in time it would be possible to detect specific antibodies against HCCs in blood or mucus samples. As for different approaches to hypothesis testing, clinical case-control studies are a conceptual possibility, in which patients, fitting the clinical profile of immune-mediated drug tolerance, would receive immunomodulatory treatment with hopes to improve drug efficacy. However, with so many possible mechanisms of tolerance development, substantial obstacles may emerge in proving a causal effect.

If the hypothesis is confirmed, it may help further elucidate the mechanisms underlying refractory diseases and contribute to the development of more effective treatment of many disorders. Furthermore, considering the range of different glucocorticoid and immunomodulatory medications already available, it may be possible to develop potent treatment strategies fairly rapidly.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Stovner LJ, Nichols E, Steiner TJ, Abd-Allah F, Abdelalim A, Al-Raddadi RM, et al. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* [Internet]. 2018 Nov 1 [cited 2020 Oct 13];17(11):954–76. Available from: <https://pubmed.ncbi.nlm.nih.gov/ezproxy.dbases.lsmuni.lt/30353868/>.
- [2] Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and Indirect Healthcare Resource Utilization and Costs Among Migraine Patients in the United States. *Headache*. 2018;58(5):700–14.
- [3] Yeh WZ, Blizzard L, Taylor B V. What is the actual prevalence of migraine? *Brain Behav* [Internet]. 2018 Jun 1 [cited 2020 Oct 13];8(6). Available from: [/pmc/articles/PMC5991594/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/ezproxy.dbases.lsmuni.lt/30353868/).
- [4] Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, Burden, and Comorbidity [Internet]. Vol. 37, *Neurologic Clinics*. W.B. Saunders; 2019 [cited 2020 Oct 14]. p. 631–49. Available from: <https://pubmed.ncbi.nlm.nih.gov/ezproxy.dbases.lsmuni.lt/31563224/>.
- [5] Bigal ME, Lipton RB. Clinical course in migraine: Conceptualizing migraine transformation. Vol. 71, *Neurology*. Lippincott Williams and Wilkins; 2008. p. 848–55.

- [6] Su M, Yu S. Chronic migraine: A process of dysmodulation and sensitization [Internet]. Vol. 14, *Molecular Pain*. SAGE Publications Inc.; 2018 [cited 2020 Oct 14]. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29642749/>.
- [7] Ferrari A, Leone S, Vergoni AV, Bertolini A, Sances G, Coccia CPR, et al. Similarities and differences between chronic migraine and episodic migraine. *Headache* [Internet]. 2007 Jan [cited 2020 Oct 14];47(1):65–72. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/17355496/>.
- [8] Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. *Headache* [Internet]. 2011 Jul [cited 2020 Oct 14];51(SUPPL. 2):77–83. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/21770929/>.
- [9] Wakerley BR. Medication-overuse headache [Internet]. Vol. 19, *Practical Neurology*. BMJ Publishing Group; 2019 [cited 2020 Oct 13]. p. 399–403. Available from: <http://pn.bmj.com/>.
- [10] D'Antona L, Matharu M. Identifying and managing refractory migraine: Barriers and opportunities? *J Headache Pain* [Internet]. 2019 Aug 23 [cited 2020 Oct 14];20(1). Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/31443629/>.
- [11] Angeles PC, Robertsen I, Seeborg LT, Krogstad V, Skattebu J, Sandbu R, et al. The influence of bariatric surgery on oral drug bioavailability in patients with obesity: A systematic review [Internet]. Vol. 20, *Obesity Reviews*. Blackwell Publishing Ltd; 2019 [cited 2020 Oct 15]. p. 1299–3A Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/31443629/>.
- [12] Darwich AS, Henderson K, Burgin A, Ward N, Whittam J, Ammori BJ, et al. Trends in oral drug bioavailability following bariatric surgery: Examining the variable extent of impact on exposure of different drug classes. *Br J Clin Pharmacol* [Internet]. 2012 Nov [cited 2020 Oct 15];74(5):774–87. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29391236/>.
- [13] Zhang J, Zhang J, Wang R. Gut microbiota modulates drug pharmacokinetics [Internet]. Vol. 50, *Drug Metabolism Reviews*. Taylor and Francis Ltd; 2018 [cited 2020 Oct 15]. p. 357–68. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30227749/>.
- [14] Choi MS, Yu JS, Yoo HH, Kim DH. The role of gut microbiota in the pharmacokinetics of antihypertensive drugs [Internet]. Vol. 130, *Pharmacological Research*. Academic Press; 2018 [cited 2020 Oct 15]. p. 164–71. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29391236/>.
- [15] Tuteja S, Ferguson JF. Gut Microbiome and Response to Cardiovascular Drugs [Internet]. Vol. 12, *Circulation: Genomic and Precision Medicine*. Lippincott Williams and Wilkins; 2019 [cited 2020 Oct 20]. p. 421–9. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29391236/>.
- [16] Rizzoli P, Loder EW. Tolerance to the beneficial effects of prophylactic migraine drugs: A systematic review of causes and mechanisms [Internet]. Vol. 51, *Headache*. Headache; 2011 [cited 2020 Oct 15]. p. 1323–35. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/21884087/>.
- [17] Williams JT, Ingram SL, Henderson G, Chavkin C, von Zastrow M, Schulz S, et al. Regulation of μ -opioid receptors: Desensitization, phosphorylation, internalization, and tolerance [Internet]. Vol. 65, *Pharmacological Reviews*. American Society for Pharmacology and Experimental Therapy; 2013 [cited 2020 Oct 21]. p. 223–54. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/21884087/>.
- [18] Akbarali HI, Dewey WL. The gut-brain interaction in opioid tolerance [Internet]. Vol. 37, *Current Opinion in Pharmacology*. Elsevier Ltd; 2017 [cited 2020 Oct 15]. p. 126–30. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29145012/>.
- [19] DosSantos MF, Holanda-Afonso RC, Lima RL, DaSilva AF, Moura-Neto V. The role of the blood-brain barrier in the development and treatment of migraine and other pain disorders [Internet]. Vol. 8, *Frontiers in Cellular Neuroscience*. Frontiers Media S.A.; 2014 [cited 2020 Oct 15]. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/25339863/>.
- [20] Wang Y, Krishnan HR, Ghezzi A, Yin JCP, Atkinson NS. Drug-induced epigenetic changes produce drug tolerance. *PLoS Biol* [Internet]. 2007 Oct [cited 2020 Oct 15];5(10):2342–53. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/17941717/>.
- [21] Montagna P. Molecular genetics of migraine headaches: A review [Internet]. Vol. 20, *Cephalalgia*. Cephalalgia; 2000 [cited 2020 Oct 15]. p. 3–14. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/10817441/>.
- [22] Sutherland HG, Griffiths LR. Genetics of Migraine: Insights into the Molecular Basis of Migraine Disorders [Internet]. Vol. 57, *Headache*. Blackwell Publishing Inc.; 2017 [cited 2020 Oct 21]. p. 537–69. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/28271496/>.
- [23] Christensen AF, Esserlind AL, Werge T, Stefánsson H, Stefánsson K, Olesen J. The influence of genetic constitution on migraine drug responses. *Cephalalgia* [Internet]. 2016 Jun 1 [cited 2020 Oct 21];36(7):624–39. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/26502740/>.
- [24] Capi M, Gentile G, Lionetto L, Salerno G, Cipolla F, Curto M, et al. Pharmacogenetic considerations for migraine therapies [Internet]. Vol. 14, *Expert Opinion on Drug Metabolism and Toxicology*. Taylor and Francis Ltd; 2018 [cited 2020 Oct 21]. p. 1161–7. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30362834/>.
- [25] Gorovits B, Baltrukonis DJ, Bhattacharya I, Birchler MA, Finco D, Sikkema D, et al. Immunoassay methods used in clinical studies for the detection of anti-drug antibodies to adalimumab and infliximab. *Clin Exp Immunol* [Internet]. 2018 Jun 1 [cited 2020 Oct 22];192(3):348–65. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29431871/>.
- [26] Ogric M, Žigon P, Lakota K, Praprotnik S, Drobne D, Štabuc B, et al. Clinically important neutralizing anti-drug antibodies detected with an in-house competitive ELISA. *Clin Rheumatol* [Internet]. 2019 Feb 14 [cited 2020 Oct 22];38(2):361–70. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30014359/>.
- [27] Dunn N, Juto A, Ryner M, Manouchehrinia A, Piccoli L, Fink K, et al. Rituximab in multiple sclerosis: Frequency and clinical relevance of anti-drug antibodies. *Mult Scler J* [Internet]. 2018 Aug 1 [cited 2020 Oct 22];24(9):1224–33. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/28762877/>.
- [28] Sethu S, Govindappa K, Alhaidari M, Pirmohamed M, Park K, Sathish J. Immunogenicity to biologics: Mechanisms, prediction and reduction [Internet]. Vol. 60, *Archivum Immunologiae et Therapiae Experimentalis*. Arch Immunol Ther Exp (Warsz); 2012 [cited 2020 Oct 22]. p. 331–44. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/22930363/>.
- [29] Song S, Yang L, Trepicchio WL, Wyant T. Understanding the Supersensitive Anti-Drug Antibody Assay: Unexpected High Anti-Drug Antibody Incidence and Its Clinical Relevance [Internet]. Vol. 2016, *Journal of Immunology Research*. Hindawi Limited; 2016 [cited 2020 Oct 22]. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/28762877/>.
- [30] Thomas LW, Lee EB, Wu JJ. Systematic review of anti-drug antibodies of IL-17 inhibitors for psoriasis [Internet]. Vol. 30, *Journal of Dermatological Treatment*. Taylor and Francis Ltd; 2019 [cited 2020 Oct 22]. p. 110–6. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29737896/>.
- [31] Wu B, Schnarr M, Devlin JL, Brown S, Yang TY. Approaches to improve drug tolerance and target tolerance in the assessment of neutralizing anti-drug antibodies. *Bioanalysis* [Internet]. 2019 [cited 2020 Oct 22];11(22):2061–74. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/31829737/>.
- [32] Xiang Y, Parnig C, Olson K, Seletskaja E, Gorovits B, Jani D, et al. Neutralizing Antibody Assay Development with High Drug and Target Tolerance to Support Clinical Development of an Anti-TFPI Therapeutic Monoclonal Antibody. *AAPS J* [Internet]. 2019 May 1 [cited 2020 Oct 22];21(3). Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30927117/>.
- [33] Gouty D, Cai CC, Cai XY, Kasinath A, Kumar V, Alvandkouhi S, et al. Recommendations for the Development and Validation of Neutralizing Antibody Assays in Support of Biosimilar Assessment. *AAPS J* [Internet]. 2018 Jan 1 [cited 2020 Oct 22];20(1). Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29285735/>.
- [34] Deisenhammer F, Jank M, Lauren A, Sjödin A, Ryner M, Fogdell-Hahn A, et al. Prediction of natalizumab anti-drug antibodies persistence. *Mult Scler J* [Internet]. 2019 Mar 1 [cited 2020 Oct 22];25(3):392–8. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29336205/>.
- [35] Mouthon L, Kaveri S V., Spalter SH, Lacroix-Desmazes S, Lefranc C, Desai R, et al. Mechanisms of action of intravenous immune globulin in immune-mediated diseases. *Clin Exp Immunol Suppl* [Internet]. 1996 [cited 2020 Oct 23];104 (SUPPL. 1):3–9. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/8625540/>.
- [36] de Sousa-Pereira P, Woolf JM. IgA: Structure, Function, and Developability. *Antibodies* [Internet]. 2019 Dec 5 [cited 2020 Oct 23];8(4):57. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29336205/>.
- [37] Vidarsson G, Dekkers G, Rispens T. IgG subclasses and allotypes: From structure to effector functions. *Front Immunol* [Internet]. 2014 [cited 2020 Oct 23];5(OCT). Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/29336205/>.
- [38] Fillatreau S. Natural regulatory plasma cells [Internet]. Vol. 55, *Current Opinion in Immunology*. Elsevier Ltd; 2018 [cited 2020 Oct 23]. p. 62–6. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30292126/>.
- [39] Roche PA, Furuta K. The ins and outs of MHC class II-mediated antigen processing and presentation [Internet]. Vol. 15, *Nature Reviews Immunology*. Nature Publishing Group; 2015 [cited 2020 Oct 23]. p. 203–16. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30292126/>.
- [40] Jurewicz MM, Stern LJ. Class II MHC antigen processing in immune tolerance and inflammation [Internet]. Vol. 71, *Immunogenetics*. Springer Verlag; 2019 [cited 2020 Oct 23]. p. 171–87. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30421030/>.
- [41] Chen CB, Abe R, Pan RY, Wang CW, Hung SI, Tsai YG, et al. An updated review of the molecular mechanisms in drug hypersensitivity [Internet]. Vol. 2018, *Journal of Immunology Research*. Hindawi Limited; 2018 [cited 2020 Oct 23]. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30421030/>.
- [42] Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. *Allergy* [Internet]. 2019 Apr 29 [cited 2020 Oct 23];74(8):all.13765. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30421030/>.
- [43] Goldman AS, Schmalstieg FC. Karl Otto Landsteiner (1868–1943). *Physician-biochemist-immunologist*. *J Med Biogr* [Internet]. 2019 May 1 [cited 2020 Oct 23];27(2):67–75. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/30421030/>.
- [44] Kuruvilla M, Khan DA. Anaphylaxis to drugs [Internet]. Vol. 35, *Immunology and Allergy Clinics of North America*. W.B. Saunders; 2015 [cited 2020 Oct 23]. p. 303–19. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/25841553/>.
- [45] Singh MK, Srivastava S, Raghava GPS, Varshney GC. HaptenDB: A comprehensive database of haptens, carrier proteins and anti-hapten antibodies. *Bioinformatics* [Internet]. 2006 Jan 15 [cited 2020 Oct 23];22(2):253–5. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/16443637/>.
- [46] Aun MV, Kalil J, Giavina-Bianchi P. Drug-Induced Anaphylaxis [Internet]. Vol. 37, *Immunology and Allergy Clinics of North America*. W.B. Saunders; 2017 [cited 2020 Oct 23]. p. 629–41. Available from: <https://pubmed.ncbi.nlm.nih.gov.ezproxy.dbazes.lsmuni.lt/28965631/>.

- [47] Muñoz-Cano RM, Bartra J, Picado C, Valero A. Mechanisms of anaphylaxis beyond IgE [Internet]. Vol. 26, *Journal of Investigational Allergology and Clinical Immunology*. ESMON Publicidad S.A.; 2016 [cited 2020 Oct 23]. p. 73–82. Available from: <https://pubmed.ncbi.nlm.nih.gov/27164622/>.
- [48] Schroeder HW, Cavacini L. Structure and function of immunoglobulins. *J Allergy Clin Immunol* [Internet]. 2010 Feb [cited 2020 Oct 23];125(2 SUPPL. 2):S41. Available from: [/pmc/articles/PMC3670108/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/20100000/).
- [49] Singhal T. A Review of Coronavirus Disease-2019 (COVID-19) [Internet]. Vol. 87, *Indian Journal of Pediatrics*. Springer; 2020 [cited 2020 Oct 23]. p. 281–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/32166607/>.
- [50] Roncati L, Ligabue G, Fabbiani L, Malagoli C, Gallo G, Lusenti B, et al. Type 3 hypersensitivity in COVID-19 vasculitis [Internet]. Vol. 217, *Clinical Immunology*. Academic Press Inc.; 2020 [cited 2020 Oct 22]. Available from: <https://pubmed.ncbi.nlm.nih.gov/32479986/>.