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Macular oedema and changes in macular thickness in multiple sclerosis patients treated with fingolimod

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Running title

Macular oedema in fingolimod-treated patients

Keywords

Macular oedema, relapsing remitting multiple sclerosis, optical coherence tomography, sphingosine, adverse effects

Abstract

Macular oedema is a known side effect to fingolimod, but changes in specific areas of the retina and the retinal nerve fiber layer are only sparsely described. Our aim was to investigate the prevalence of macular oedema and characterize macular changes after initiation of fingolimod based on routine ophthalmological examinations in all consecutive patients treated at our hospital. We evaluated macular thickness change from baseline to 3-4 months after initiation of treatment. Central retinal thickness, total macular volume, total macular thickness, average thickness and inner-/outer macular thickness was automatically measured using optical coherence tomography (OCT). A total of 190 eyes completed the study and none of those developed visible macular oedema. All macular areas showed a small, but statistically significant increase in thickness. Total macular volume increased by a mean of 0.05 mm^3 ($p = < 0.001$). Mean best-corrected visual acuity only changed by 0.03 ($p = 0.074$). We observed a minimal change in macular thickness and no clinically relevant affection on visual acuity after 3-4 months of fingolimod treatment. Thus, our results do not underpin the need for routine screening for macular oedema in asymptomatic MS patients without diabetes or uveitis receiving 0.5 mg fingolimod daily.

Introduction

Fingolimod (Gilenya) is a spingosine-1-phosphate ($S1P_1$) receptor modulator acting on G-protein-coupled $S1P_1$-receptors on peripheral lymphocytes by retaining both naive- and central memory T-cells [1]. Fingolimod was registered in 2011 for use in relapsing remitting multiple sclerosis (RRMS), primarily as second-line therapy or in patients with rapidly evolving severe disease [2]. The recommended dose in adults is 0.5 mg once daily [2].

Two cases of macular oedema occurring in early studies of fingolimod with daily doses of 2.5 and 5 mg for renal transplant recipients [3] triggered the awareness of this complication, and led to the introduction of ophthalmic examinations of study patients [4]. Thus, macular oedema was found in up to 3.4% of patients treated with 5 mg with a trend towards a dose-related frequency [3, 5]. Later, 19 cases of macular oedema were identified amongst 2615 patients in the clinical trials FREEDOMS [6] and TRANSFORMS [7] and their extensions evaluating fingolimod in lower doses for RRMS [4]. Again, the occurrence was dose-related with a prevalence of 1.2 % and 0.3% in patients receiving 1.25 mg and 0.5 mg daily, respectively.

The manufacturer of Gilenya recommends ophthalmic examinations after 3-4 months' treatment in all patients as well as before initiation in patients with a prior history of uveitis or diabetes [2]. However, a baseline and 3-4-month follow-up ophthalmological examination including optical coherence tomography (OCT) has routinely been performed in all patients treated with fingolimod at Aalborg University Hospital since 2011. The aim of the present study was to investigate the outcome of these ophthalmic examinations in order to evaluate the prevalence of macular oedema and to investigate changes in the macula and optic disc nerve fibre layer.

Methods

Patients

We identified all patients treated with fingolimod at the department of Neurology, Aalborg University Hospital, between 1 January 2011 and 1 May 2018. All participants met the revisited 2005 International Panel MS diagnostic criteria [8]. In accordance with the screening program, the patients had a macular OCT and when possible an optic disc OCT performed right before and 3-4 months after initiation of treatment with fingolimod. We included those with a valid OCT at both visits. Eyes with a known retinal or macular disease expected to affect macular thickness per se or eyes that had undergone surgery less than 6 months prior to treatment with fingolimod or during the observation period were excluded from the study.

Collected data

Central retinal thickness (CRT), total macular volume (TMV), total macular thickness (TMT), average thickness as well as inner and outer macular thickness were automatically calculated by the TOPCON ImageNet 6 software. Scans were obtained by trained personnel using TOPCON Triton Swept source OCT, and data from both eyes, if possible, were analysed. The average of the four inner macular sectors and the four outer macular sectors were calculated and defined as inner and outer ring thickness. There is no defined cut-off value to signify minimally, clinically relevant change in macular thickness. Visual acuity served as an indicator of clinical significance of possible changes in macular thickness. Age, race, former MS treatment, other eye disease (e.g. optic neuritis, a history of uveitis, diabetic

retinopathy or other retinal disease), refraction and medication apart from fingolimod were also obtained from the patient journal. Macular oedema was defined as visible intraretinal cysts or subretinal fluid on OCT.

In accordance with Danish legislation (Act on Research Ethics Review of Health Research Projects § 14 subsection 2, dated 15 September 2017 and the Danish Health Act § 46 subsection 2, dated 2 November 2018), the Danish Patient Safety Authority approved the project including transmission of data from the patient records. The study was registered at the Danish Data Protection Agency and data were handled in accordance with the general data protection regulation. The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [9].

Statistics

Data were entered in REDCap™(Vanderbilt, USA) electronic data capture tools hosted at Aalborg University and statistical analysis was performed using STATA version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC). Distribution of data was evaluated using histograms and q-norm plots. Parametric data are presented as means with 95% confidence intervals (95% CI) or means ± standard deviations (SD) and non-parametric data as medians with interquartile ranges. To evaluate mean difference in OCT measurements before and 3-4 months after initiation of fingolimod treatment, we used a *paired t-test* in data following a normal distribution. Non-parametric data were analysed using *Wilcoxon signed rank test*. To evaluate whether patients with other eye disease were more prone to develop changes in OCT measurements, we compared the mean change in each parameter between eyes with a known diagnosis of the relevant disease to eyes without the diagnosis, using *Student's t-test*.

Results

We identified a total of 138 patients or 276 study eyes treated with a standard dose of 0.5 mg fingolimod daily. Demographics and clinical features of the population are shown in Table 1. Nineteen patients had only one of the two examinations performed, and twenty-three patients did not show up at any of the planned examinations because they either changed department during the period, missed their appointments or were never referred to the department of ophthalmology. Two eyes were excluded as a result of concomitant retinal/macular disease and poor OCT quality (Figure 1). In twelve eyes, the software was unable to calculate average macular thickness and TMV, mainly because of reduced scan quality due to opacities in the anterior part of the eye.

None of the eyes showed visible macular oedema at baseline or follow-up. When considering all eyes, both average thickness, CRT, TMV, TMT and inner-/outer macula changed significantly (Table 2). The inner macula seemed slightly more prone to increase in thickness compared to the outer part. TMV increased by a mean of 0.05 (0.03, 0.07) mm^3 ($p = < 0.001$). In percentages TMV, average thickness and CRT increased by 0.68%, 0.69% and 1.06%, respectively. A total of 114 eyes experienced an increase in TMV while 64 decreased or stayed unchanged (Figure 2).

Mean best-corrected visual acuity (BCVA) at baseline was 1.04 Snellen and 1.01 at 3 months yielding a non-significant mean change of 0.03 ($p = 0.074$).

Eleven eyes (5.8%) were reported having visual disturbances during the observation period. In spite of the symptoms, only one eye experienced a decrease in BCVA > 1 line (from 1.4 to 0.4). Seven of the eyes with visual disturbances had a prior history of optic neuritis and a small increase in either TMV or average thickness occurred in four of those.

Eight eyes (four patients) in total had either a previous history of uveitis, a diagnosis of diabetes or cataract surgery done prior to fingolimod treatment and none of them showed any sign of macular oedema or significant macular thickness difference after 3-4 months compared to baseline. Eleven patients were registered using medication other than fingolimod at the time of fingolimod initiation. Forty-two patients had a history of previous optic neuritis. Comparing the macular changes in the optic neuritis group to the non-optic neuritis group demonstrated no significant difference in any of the given parameters.

Discussion

To our knowledge, this is the largest study of macular findings in real-world consecutive fingolimod-treated patients so far. The main findings are that no patients developed visible macular oedema and that both thickness and volume of the macular area increased during 3-4 month follow-up after initiation of treatment. Although statistically significant, the little change in macular thickness we found is less than the normal inter-individual variance, [10] and we do not consider it clinically relevant. In fact, we found no relation between change in thickness and reported visual disturbance or change in BVCA, and the mean BCVA for the whole group was normal for this age group at both baseline and 3-4 month follow-up. Only a few patients reported visual disturbances and the majority of those had a history of optic neuritis prior to fingolimod treatment.

The findings that none of our patients developed macular oedema is in agreement with other studies showing a frequency of macular oedema of 0.3% in patients treated with the 0.5 mg dose used in RRMS [4]. The rare occurrence is supported by several post marketing studies emerging in recent years mentioning a total of eight cases of macular oedema amongst almost 2000 patients [11-20]. The finding of small increases in macular thickness and volume is also in line with a previous study of Nolan et al. that showed a small but significant difference in macular volume between MS patients treated with fingolimod and patients never treated with fingolimod [21]. The study included 30 patients in each group and not unlike our results, the TMV increased by 0.03 μm in the fingolimod group compared with no change in the control group. Another recent study, published in 2018 by Fruschelli et al [22]. with a population comparable to ours, found no statistically significant change in TMV at three, six or twelve months after initiation of fingolimod. Importantly, there was no significant change in visual acuity during the observation period in any of the two studies and in general the changes in macular thickness seemed to be small.

It is known that $S1P_1$ receptors are important in promoting endothelial barrier integrity. The opposite is true with fingolimod, which is acting as an $S1P_1$ antagonist leading to cell cytoskeleton rearrangement, increased vascular permeability and interrupted intercellular adhesion [23,24]. This may suggest that fingolimod is a main contributor to increased retinal thickness. Interestingly though, macular oedema was also found to occur in 0.6% of patients treated

with placebo in the FREEDOMS trial as compared to 0.8% in the actively treated group [4], suggesting that macular oedema is not exclusively a problem in fingolimod-treated patients. In continuation hereof, it has been discussed whether increase in retinal thickness and macular oedema is a side effect of fingolimod or simply a consequence of MS activity itself. In fact, up to 5% of MS patients in general show micro cystic macular oedema and the severity of the oedema corresponds to the severity of MS [25]. After all, the change in therapy to fingolimod comes as a consequence of disease activity and is therefore a possible confounder. An RCT from 2014 by Ocwieja et al. looked at healthy persons treated with either fingolimod 0.5 mg, 1.25 mg or placebo and found no change in macular thickness in either of the groups [26]. However, their observation period was only 4 weeks, but to some extent, it is clearly questioning the role of fingolimod in retinal thickness changes. Furthermore, it has been suggested that the increase in retinal thickness is not necessarily a negative side effect but rather a neuroprotective effect of S1P-receptor-modulators in CNS [27-29]. Altogether, it is difficult to determine the isolated role of fingolimod in the pathogenesis of the small retinal changes we observed. As mentioned, altered disease severity may also play a role, and the lack of a control group in order to address this is a limitation of our study.

In order to evaluate the value of the ophthalmological examinations at 3-4 months after fingolimod initiation, it is important to know whether retinal changes and macular oedema might appear later on, beyond the 4 months of our study. The findings by Zarbin et al. showed that most cases of macular oedema in their study presented themselves with symptoms within 3-4 month of treatment [4]. Furthermore, the extension studies in both FREEDOMS and TRANSFORMS observed fingolimod-treated patients for 24 and 48 months, respectively, and found no increase in cases of macular oedema during this period [30, 31]. This gives us reason to believe that most of the presumed fingolimod-induced retinal changes is happening during the first few months. Hence, it seems safe to perform the ophthalmologic screening at this time. However, the examinations are also time-consuming, and it can be speculated how much safety these visits add to the treatment of the RRMS patients, and if they are worth the costs. The low prevalence implies that 300 examinations can be expected in order to identify one case of macular oedema. Furthermore, in the study by Zarbin et al., the majority of patients with macular oedema presented with symptoms [4], and the condition was reversible upon withdrawal of fingolimod in more than 80% of cases. Diabetes, a history of uveitis and age above 41 years have been identified as risk factors. That taken into account, it may be considered to restrict the ophthalmic examinations to those with symptoms or with risk factors in order to allocate resources more appropriately.

There are a number of limitations to our study. For one thing, we could not compare the observed small changes in macular thickness observed after 3-4 months of fingolimod treatment with an age-matched control group, because we do not routinely perform OCT scans repeatedly with 3-4 month intervals in MS patients not treated with fingolimod Also, it is an important limitation of this study that it is not possible to objectively determine whether changes in OCT are entirely due to the effect of fingolimod. An influence of e.g. disease activity and concomitant symptomatic treatment with other medications cannot be excluded. Concomitant medication was only noted in the patient records of eleven patients, but we cannot be ascertained that all medications prescribed by e.g. general practitioners were listed here. Furthermore, one third of all treated patients were lost to follow-up and we do not know the ophthalmological outcome in these cases. Finally, the population is rather small to conclude on the prevalence of macular oedema, and there were very few patients with diabetes and uveitis in our population. Thus, the effect of

fingolimod on macular thickness in patients with these risk factors cannot be appreciated from our results. However, to our knowledge, our study provides the largest set of OCT data from post marketing fingolimod-treated patients so far.

Conclusions

Macular oedema did not develop in any of the studied patients. We found a small statistically significant increase in macular thickness, which did not affect the visual acuity or visual perception. Altogether, we do not consider the change clinically relevant and a causative role of fingolimod is not certain. Thus, our results do not underpin the need for routine screening for macular oedema in asymptomatic MS patients without diabetes or uveitis receiving 0.5 mg fingolimod daily.

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Table 1

Demographics and clinical features

Age, years mean ± SD		42.3 ± 10.7
Female, n (%)		63 (66.3)
Race, *n* (%)	Caucasians	94 (98.9)
	Indian	1 (1.1)

Refraction*, mean ± SD	Spheric	-0.73 ± 2.01
	Cylinder	-0.81 ± 0.72
Former ON (%)		21 (22.1)
Cataract surgery (%)		1 (1.1)
Former MS treatment (%)	Interferon β-1a (Avonex/Rebif)	62 (65.3)
	Glatirameracetat (Copaxone)	22 (23.2)
	Natalizumab (Tysabri)	17 (17.9)
	Teriflunomid (Aubagio)	14 (14.7)
	Other	9 (9.5)

Abbreviations: SD, standard deviation; ON, opticus neuritis; MS, multiple sclerosis. * Measured in dioptries

Table 2

Average retinal thickness comparison between baseline and follow-up

	n (eyes)	Mean pre ± SD	Mean post ± SD	Mean difference (95% conf.interval)	p-Value
TMV (mm^3)	178	7.38 ± 0.41	7.43 ± 0.42	0.05 (0.03, 0.07)	< 0.001
Avth *(μm)*	178	261.0 ± 14.5	262.8 ± 14.8	1.87 (1.00, 2.74)	< 0.001
CRT *(μm)*	190	235.0 ± 19.4	237.5 ± 19.9	2.47 (0.96, 3.97)	0.001

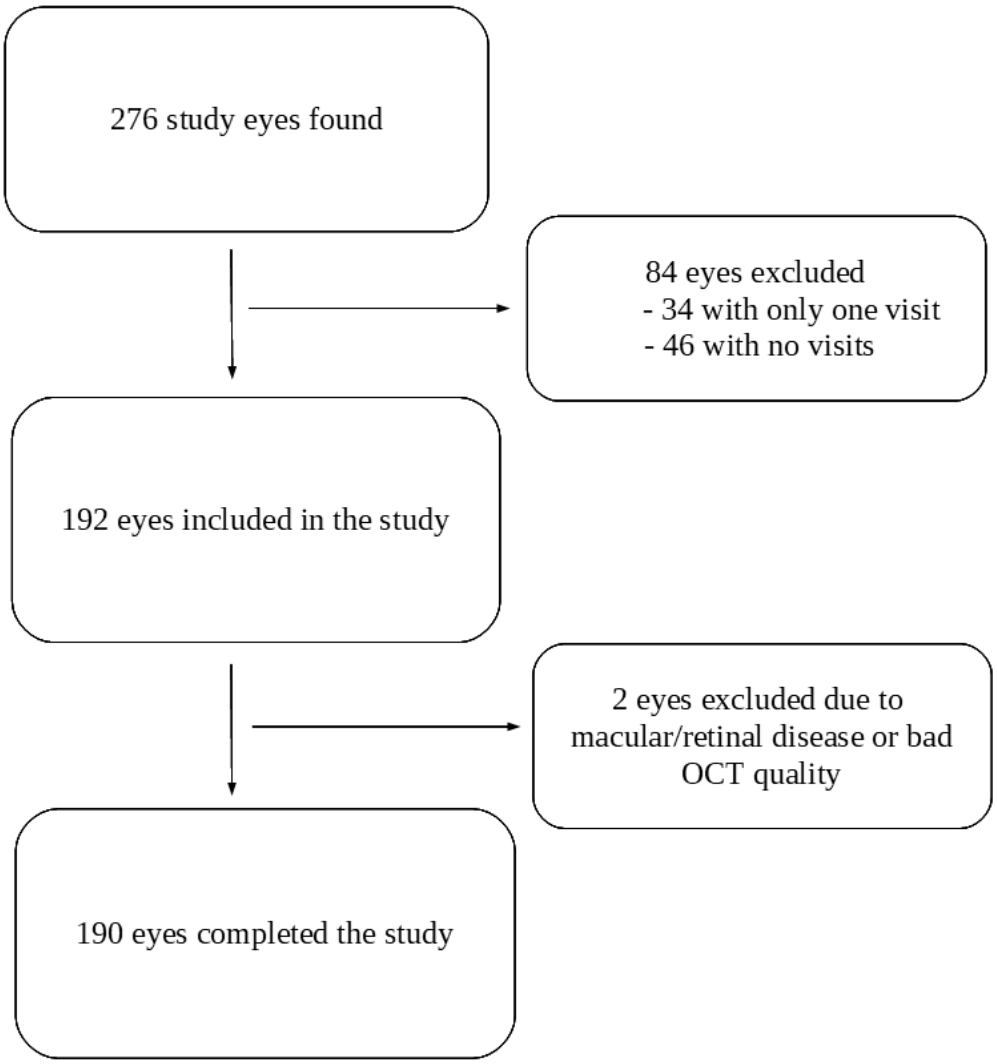
TMT *(µm)*	190	2402 ± 135	2422 ± 141	19.7 (11.6, 27.7)	< 0.001
Outer ring *(µm)*	190	1010 ± 63.4	1015 ± 63.8	4.85. (0.19, 9.52)	0.042
Inner ring *(µm)*	190	1157 ± 71.4	1169 ± 73.3	12.3 (7.81, 16.9)	< 0.001

Abbreviations: pre, values at baseline; post, values 3-4 months after initiation of fingolimod treatment. SD; standard deviation; TMV, total macular volumen; Avth, average thickness; CRT, central retinal thickness; TMT, total macular thickness; tot, total; sup, superior, tem, temporal; inf, inferior; nas, nasal

Figure legends

Figure 1
Flow-chart, showing inclusion and exclusions.

Figur 2
Bar chart showing numbers of eyes increasing (>0) or decreasing (≤0) in total macular volume (TMV) 3-4 months after fingolimod treatment. 114 eyes increased and 64 decreased/stayed unchanged.



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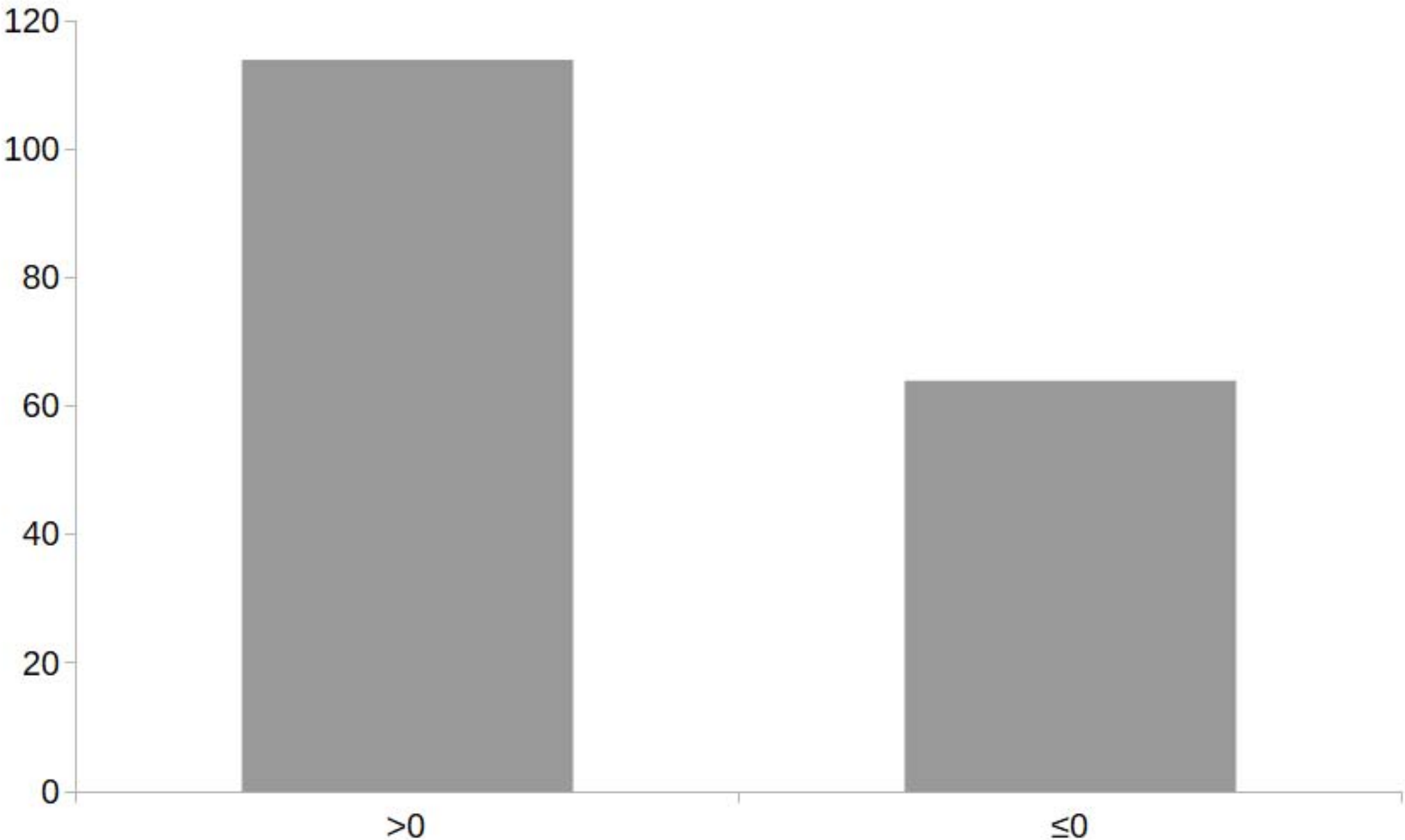
120
100
80
60
40
20
0
>0
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