

Erectile dysfunction medical treatment with phosphodiesterase 5 inhibitors (PDE5i) in patients with retinitis pigmentosa and side effects

KEY WORDS: *Erectile dysfunction; Medical treatment; Side effects.*

Submitted 29 April 2020; Accepted 10 June 2020

To the Editor

Retinitis pigmentosa represents a heterogeneous group of degenerative hereditary pathologies of the retinal photoreceptors, some forms mainly affect the cones and others the rods (1). The prevalence of the disease is of 1 case per 3000-5000 inhabitants (1), in 80-90% of cases these are forms with prevalent involvement of the rods (RCD) and in 10-20% of cases of forms with prevalent involvement of the cones (CRD) (2). In 85% of the cases these are isolated forms, while in 15% of syndromic forms (2), the most common syndromic form is Usher's syndrome, in which retinitis pigmentosa is associated with neurosensory deafness (3). An extensive search of Medline, Embase and Scopus databases was conducted to retrieve English-language articles published up to 31 Dec 2019, assessing side effect of PDE5i. The protocol was performed according to the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) statement. All studies have been included. Congress meetings, editorial comments and review papers were excluded: Further exclusion criteria were full texts not available in English. Two reviewers (G.I.R. and A.C.) independently assessed the eligibility of the identified papers and any disagreements were discussed with a third reviewer (G.M.).

In the early stages of RCD disease patients show predominantly decreased night and peripheral vision, associated with photophobia. Patients with CRD complain of photophobia and reduced central vision. In both cases, disease evolution and specific symptoms are difficult to predict and depend on genetic and environmental factors.

PDE-6

Phosphodiesterase 6 is an isoenzyme of PDE that is found in the retina and is involved in the transduction of the signal, some forms of retinitis pigmentosa are related to mutations on this enzyme (4). PDE5 is the molecular target of several drugs used in the treatment of erectile dysfunction, but some of these drugs have off-target actions on PDE6 and may therefore be contraindicated (2).

PDE5 Inhibitors (5-7)

Phosphodiesterase is an enzyme responsible for the hydrolysis of cGMP, a molecule that allows the erection of the penis thanks to its vasodilatory action on smooth vascular muscle cells. The smooth muscle cells of the corpora cavernosa of the penis express the isoenzyme PDE5. Inhibitory drugs specific to PDE5 are used for the treatment of erectile dysfunction: by inhibiting the enzyme they stop the hydrolysis of cGMP and thus promote vasodilation and erection. Off-target action of PDE5 inhibitors can result in several adverse reactions. Of particular interest are the adverse reactions related to the action on retinal PDE6, which may contraindicate treatment in patients with retinitis pigmentosa, where the functioning of the photoreceptors is already impaired (Tables 1, 2).

Sildenafil

Sildenafil is the most used inhibitor of PDE5, its action is not entirely specific for PDE5 but has a slight affinity for PDE6 retinal, in fact 9% of patients report among the adverse reactions, photosensitivity and alterations in color vision (5, 8). The intake of sildenafil may cause transient alterations in the electroretinogram, so it is not recommended for patients with retinitis pigmentosa (4, 5).

Verdenafil

Verdenafil is a molecule similar to sildenafil but more potent (7) and more selective than sildenafil, so higher doses are needed for adverse reactions related to the action on PDE6 to occur, which are therefore very rare.

Tadalafil

Tadalafil has a chemical structure different from that of sildenafil and verdanafil, it has very little action on PDE6 so it does not cause adverse reactions for off-target effect on that isoenzyme (9).

Avanafil

Avanafil has recently been approved for the treatment of erectile dysfunction, it is a very selective pyrimidine derivative

No conflict of interest declared.

for PDE5, which therefore does not cause adverse reactions related to the action on PDE6 (10, 11). Following a single 200 mg dose of Avanafil, no changes in colour perception were detected, however, the observation was made in a small sample and the data may not be significant. Similar results were also obtained in larger studies with larger doses of medication (12).

Other adverse reactions

Other side effects were headache, dyspepsia, skin flush for sildenafil (4); headache, dyspepsia, skin flush, rhinitis, lengthening of QT for vardenafil (13, 14); headache, dyspepsia, back pain for tadalafil (5); headache, skin flush, nasal congestion, muscle cramps, postural hypotension for avanafil (10, 11).

Although there is no evidence in the literature that the administration of PDE5i in patients with retinitis pigmentosa may or may not lead to an aggravation of the disease, in the light of the knowledge on the pharmacodynamics of PDE5i and on the etiopathogenesis of retinitis pigmentosa, it seems appropriate, as a precaution, to avoid administering to these patients the least selective drugs for PDE5 and opt instead for the most selective ones. In case of patient presenting retinitis pigmentosa and organic or post-operative erectile dysfunction, the possibility of PDE5i treatment should not be excluded. This kind of patient should be analyzed and should undergo specific genetic tests to assess the presence or absence of mutations in gene coding for PDE6 expressed at retinal level. In conclusion the presence of PDE6 mutation allows us to avoid oral treatment with PDE5i.

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