Literature Review of Recombinant Tissue Plasminogen Activator Used for Recent-Onset Submacular Hemorrhage Displacement in Age-Related Macular Degeneration

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Key Words

Age-related macular degeneration • Recombinant tissue plasminogen activator • Hemorrhage

Abstract

Aims: To review and discuss the literature on recombinant tissue plasminogen activator (rtPA) for the treatment of a recent-onset submacular hemorrhage in patients with age-related macular degeneration. **Methods:** The administration technique of rtPA, the use of additional gas and vascular endothelial growth factor inhibitors (anti-VEGF), and the displacement rate of submacular hemorrhage and complications were noted from published reports, and a case series from the Rotterdam Eye Hospital (REH). **Results:** 38 studies with a total of 1,185 patients (1,176 eyes), and 28 patients from the REH were analyzed. Several methods for rtPA administration are available, which can be divided into two groups: submacular rtPA administration with vitrectomy; or intravitreal rtPA administration without vitrectomy. In both groups, the administration of gas and/or anti-VEGF agents could be additional. There appears to be no clear difference in complete displacement or complication rate between the more or the less invasive treatment groups. **Conclusion:** Although intravitreal injection of rtPA and gas only was reported to be

as effective as subretinal rtPA with vitrectomy and gas, recent studies tend to use vitrectomy. These data underscore the need for a randomized controlled trial to choose the most effective and safe method of rtPA administration.

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Introduction

Intravitreal injection of vascular endothelial growth factor inhibitors (anti-VEGF) is the standard of care for patients with exudative age-related macular degeneration (AMD). However, anti-VEGF injections are not effective in restoring or improving visual acuity (VA) when a large submacular hemorrhage is present. SMH is a relatively common and severe complication of exudative AMD, particularly in patients taking anticoagulant medications [1]. It leads to immediate and extensive, albeit sometimes reversible, loss of visual acuity, and if left untreated, can cause irreversible damage to the retinal pigment epithelium (RPE) cells and retina [2, 3].

Heriot firstly reported a minimally invasive pneumatic displacement method: intravitreal injection of rtPA and gas, in which the gas bubble and gravity combine to displace the hemorrhage inferiorly and away from the

submacular region. This allows for extrafoveal resorption of the hemorrhage which causes less functional damage to the central VA [4]. Another, more invasive, method of rtPA-assisted displacement of a hemorrhage has since been described: vitrectomy, followed by subretinal rtPA injection, and a gas [5, 6] or air [7–9] tamponade.

Both minimally invasive and invasive methods were, in later studies, combined with anti-VEGF therapy [10–14], allowing for simultaneous treatment of the causative choroidal neovascularization [11].

These displacement methods are primarily intended for hemorrhages of recent onset, i.e. hemorrhages existing for approximately 14 days or less, as the hemorrhage causes progressively severe damage to the retina [2, 3], and older hemorrhages may become more difficult to displace. However, in many studies included in this review, the displacement methods have been used for patients with older hemorrhages as well.

The results of a large number of uncontrolled studies suggest that patients with recent onset submacular hemorrhage, whose prognosis might have been dire in the past, can now be effectively treated with relatively safe surgical interventions. The primary difference between the various studies is whether rtPA and anti-VEGF are administered intravitreally, in which case no further surgical procedure is employed, or subretinally, in which case vitrectomy is required. The effectiveness of the different rtPA approaches used seems to be comparable, but the complication rate is likely to be higher if more invasive methods are used.

Besides the treatment modality, there are several variables that may affect the treatment outcome. These include the thickness [15] and size [16, 17] of the hemorrhage, and elevation of the retina by the hemorrhage [15, 17].

The recent trend has been toward the subretinal administration of rtPA after vitrectomy, followed by gas tamponade. This has been shown to be an effective combination. However, it remains uncertain whether the primary mechanism for displacement of the hemorrhage is a pushing or rolling action of a partial tamponade [4] or whether it is the effect of gravity working upon the hemorrhage in the context of a complete tamponade [18, 19].

Further, a randomized, controlled trial might help to elucidate the relative advantages and disadvantages of the more invasive method for rtPA administration, involving vitrectomy, submacular administration of rtPA and gas tamponade as compared to the less invasive method, involving the simple intravitreal injection of rtPA and gas tamponade. Both arms of the study should then also in-

clude injection of an anti-VEGF agent intravitreally peroperatively. As part of the preparation for this controlled trial, we analyzed the feasibility (in terms of hemorrhage displacement) and in especially the safety (complication rates) of the different procedures using information derived from existing clinical reports as well as from data of the Rotterdam Eye Hospital.

Patients and Methods

Literature Search

Literature searches of the PubMed database were last conducted on January 10th, 2012. The first PubMed search was conducted using the following key words: 'recombinant tissue plasminogen activator AND gas AND age related macular degeneration'. The second search was conducted with the following key words: 'submacular hemorrhage AND gas'. The third search was conducted with the following key words: 'recombinant tissue plasminogen activator AND age related macular degeneration AND air', and the fourth search string with the key words 'tissue plasminogen activator AND age related macular degeneration'. The searches were limited to articles published in English and German. No date restrictions were employed. We also searched the reference lists of the studies included in the review for other potential inclusions. We specifically searched for studies that used either rtPA or gas tamponade only, or a combination of both, as a method to remove a submacular hemorrhage for AMD patients. These methods could be combined with vitrectomy and/or the administration of anti-VEGF agents. All studies had to at least include patients with AMD, and the total number of patients in the study had to be 5 or more. For studies in which rtPA treatment was compared with bevacizumab or gas only or gas and bevacizumab combined, or natural history or manual removal of the hemorrhage, only the patients who were included in the rtPA arm of the study were included in the analysis.

The following data were entered into a database: the number of patients included in the study; the etiology of the submacular hemorrhage; whether treatment included vitrectomy; the type of tamponade used; whether rtPA and/or anti-VEGF agents were used and their method route of administration (submacular or intravitreal); the rate of hemorrhage displacement and its extent, defined as no (complete displacement) or some (partial displacement) blood left in the foveal area; percentage of eyes with a final VA >20/200; percentage of eyes which gained 2 lines (Early Treatment Diabetic Retinopathy Study [ETDRS] or Snellen) or more in VA; and number of complications, such as recurrent subretinal/submacular hemorrhage, (exudative inferior) retinal detachment, proliferative vitreoretinopathy (PVR) or vitreous hemorrhage. When VA results were presented in a table but the authors themselves did not calculate VA improvement rates or percentages, an attempt was made to do so, if the available data allowed. All VA measurements were converted into logMAR values for statistical analysis in which 'finger counting' at 60 cm was transposed into logMAR 2, and 'hand motion' into logMAR 3 [20]. These same parameters were entered into the table of our own retrospective case review of patients with SMH due to AMD who were treated in the REH between July 2008 and February 2011.

Patients of the REH

The sole inclusion criterion for our own patient group was neovascular AMD complicated by SMH involving the fovea. The sole exclusion criterion was an SMH whose etiology was a disease other than AMD. Pre- and postoperative examinations consisted of a standard ophthalmologic examination supplemented by fundus photography, optical coherence tomography and, when choroidal neovascularization was suspected, fluorescein and/or indocyanine green angiography. The following surgical technique was employed: after induction of a posterior vitreous detachment, a complete pars plana vitrectomy was performed. We used a 23 G cannula with a 41 G tip, connected by tubing to a tuberculin syringe (Dutch Ophthalmic Research Center [DORC], Zuidland, The Netherlands), filled with the rtPA solution. Once the 41 G tip was inserted through the retina, the assistant would inject 0.1 ml of fluid (20 µg/0.1 ml rtPA (Actilyse, Boehringer Ingelheim, Ingelheim, Germany) into the subretinal space or clot, creating a local retinal detachment encompassing (a part of) the blood hemorrhage. After rtPA injection, the internal limiting membrane (ILM) was peeled, starting from the injection site, which was most frequently created at the superior edge of the hemorrhage. This peeling was performed to prevent formation of a macular pucker or PVR after surgery. After fluid/air exchange, the vitreous cavity was filled with a 15% sulfur hexafluoride (SF6) or 10% perfluoropropane (C3F8) gas/air mixture. Patients were instructed to maintain an upright, lateral or prone position, depending on the intended direction of hemorrhage displacement.

Results

Literature Search

The PubMed first search string, with the key words 'recombinant tissue plasminogen activator AND gas AND age related macular degeneration', retrieved 50 articles, of which 30 were considered to be relevant. The second search string, with the key words 'submacular hemorrhage AND gas' retrieved 60 articles, of which 4 were both relevant and had not been identified by the previous search string. The third search string with, the key words 'recombinant tissue plasminogen activator AND age related macular degeneration AND air', retrieved 9 articles, of which 3 were relevant and new. The fourth search string with the key words 'tissue plasminogen activator AND age related macular degeneration' retrieved 113 articles, of which 1 was relevant and new. The reference lists of the studies included in the review for other potential inclusions did not add any new relevant studies. This search resulted in a total of 38 articles that were deemed to be relevant to the topic. These 38 studies had included a total of 1,185 eyes (1,176 patients) which were deemed eligible for further study according to the inclusion criteria and were entered into the database (table 1).

Surgical Technique

Several techniques for the treatment of acute submacular hemorrhage were described and are summarized in table 1. In three studies, only intravitreal gas injection was used in an attempt to displace the hemorrhage [21–23]. Four studies employed either gas injection or both rtPA and gas injected intravitreally, depending on the study arm [24–27]. One of these studies administered anti-VEGF only postoperatively in 8 out of 53 patients [26]. One study employed intravitreal rtPA with and without intravitreal gas injection [28]. Fifteen studies reported intravitreal injection of both rtPA and gas [29–43]; one of these 15 studies incorporated the results of its own, older article [32, 39]. Five studies reported intravitreal rtPA and intravitreal anti-VEGF agents and gas injections [11–13, 44, 45]. In 4 of these 5 studies, next to the rtPA, anti-VEGF agents were administered during surgery; in the fifth study, anti-VEGF was administered during the 4- to 6-week interval after surgery, if clinically indicated [45]. Four other studies reported the combination of vitrectomy, subretinal rtPA application and air tamponade [7–9, 46]; in one of these studies, intravitreal anti-VEGF agents were only administered postoperatively, if required by the study protocol [46]. Two studies administered subretinal rtPA combined with vitrectomy and gas tamponade [5, 47]. Two studies retrospectively compared subretinal versus intravitreal rtPA administration, both combined with vitrectomy and gas injection [6, 10]; patients in one of these two studies also received intravitreal anti-VEGF [10]. Two studies, one of which included long-term results of the patients of the other, earlier study, reported subretinal rtPA and also subretinal anti-VEGF administration during surgery, with a gas tamponade, followed by intravitreal anti-VEGF after surgery [14, 48] (table 1).

Analysis of the Displacement and Complication Rate in Literature

To describe the difference between administration techniques of rtPA and gas or air tamponade, we clustered only the (parts of) the studies which used rtPA and gas or air, plus our own study, into four groups. As complication or displacement rates were not consistently reported, or not specified between different subgroups in a study, and not all studies used rtPA in each patient, not all applicable studies could be included in either the analysis of displacement or complication rates. Thus, of the 1,185 eyes out of the studies from the literature, the data of 221 eyes could not be included in this analysis.

Table 1. Review of 38 studies from the literature and one study from The Rotterdam Eye Hospital, The Netherlands

Reference	Number of eyes treated with rtPA	Etiology of hemorrhage	Vitrectomy	Tamponade	rtPA	Anti-VEGF
Gas only						
Ohji, 1998 [21]	5 gas only	AMD (4), RAM (1)	–	Gas (C3F8)	–	–
Gopalakrishnan, 2007 [22]	20 gas only	AMD (5), polypoidal choroidal vasculopathy (8), extramacular CNVM and ruptured macroaneurysm (3), other (3)	–	Gas (C3F8)	–	–
Ron, 2007 [23]	24 gas only	AMD	–	Gas (C3F8: n = 11; SF6: n = 13)	–	–
Combined studies: gas only or intravitreal rtPA with gas						
Yang, 2005 [27]	8 rtPA and gas, 16 gas only	AMD (18), traumatic choroidal rupture (2), RAM (2), IPCV (1), proliferative diabetic retinopathy (1)	–	Gas (C3F8: n = 19; SF6: n = 5)	rtPA IV/ gas only	–
Fang, 2009 [25]	28 rtPA and gas, 25 gas only	AMD	–	Gas (C3F8: n = 5; SF6: n = 48)	rtPA IV/ gas only	–
Çakir, 2010 [24]	7 rtPA and gas, 14 gas only	AMD (16), myopic CNV (2), RAM (2), trauma (1)	–	Gas (C3F8)	rtPA IV/ gas only	7/7 bevacizumab postoperative
Mizutani, 2011 [26]	40 rtPA and gas, 13 gas only	AMD (39), RAM (14)	–	Gas (SF6)	rtPA IV/ gas only	8 eyes postoperative (6 ranibizumab, 2 pegaptanib)
Combined study: intravitreal rtPA only or intravitreal rtPA with gas						
Tsyanava, 2011 [28]	64 rtPA and gas, 46 only rtPA, no gas	AMD	–	Gas (not specified)/ none	IV	–
Intravitreal rtPA and gas						
Hesse, 1999 [33]	11	AMD	–	Gas (C3F8: n = 3; SF6: n = 7; C2F6: n = 1)	IV	–
Hassan, 1999 [31]	15	AMD (13), RAM (1), trauma (1)	–	Gas (C3F8: n = 7; SF6: n = 8)	IV	–
Meier, 1999[35]	22	AMD	–	Gas (SF6)	IV	–
Buhl, 1999 [37]	53	AMD (47), RAM (6)	–	Gas (SF6)	IV	–
Framme, 2000[38]	8	AMD	–	Gas (SF6)	IV	–
Krepler, 2000 [34]	11	AMD	–	Gas (SF6)	IV	–
Handwerker, 2001[30]	14	AMD	–	Gas (C3F8)	IV	–
Hattenbach, 2001 [32]	43	AMD	–	Gas (SF6)	IV	–
Hattenbach, 2002* [39]	25	AMD	–	Gas (SF6)	IV	–
Schulze, 2002 [36]	67	AMD	–	Gas (C3F8/SF6)	IV	–
Tsai, 2003 [42]	15	AMD	–	Gas (C3F8)	IV	–
Ratanasukon, 2005 [41]	19	AMD (15), idiopathic choroidal neovascularization (2), traumatic (1), valsalva retinopathy (1)	–	Gas (C3F8: n = 7; SF6: n = 12)	IV	–
Chen, 2007 [29]	104 (19 lost to follow-up and therefore excluded)	AMD (88), high myopia (4), RAM (5), trauma (3), IPCV (2), angioid streaks (1), intraoperative complications (1)	–	Gas (C3F8: n = 56; SF6: n = 47), 1 air	IV	–

Successful displacement (%)	Final VA >20/200 (%), follow-up	Eyes gained 2 (ETDRS or Snellen) lines or more (%), follow-up	Complications
3/5 (60%)	3/5 (60%) (1 week to 13 months' follow-up)	5/5 (100%) 2 or more ETDRS lines increase (1 week to 13 months' follow-up)	Vitreous hemorrhage (1), retinal detachment (1)
Complete: 10/20 (50%), partial: 6/20 (30%)	Final VA 20/63 or better in 12/20 patients (60%), non-AMD patients (median of 6 months, range 3–42 months)	Mean best-corrected VA improved from 1.6 to 0.72 logMar (9 ETDRS lines), at 3 months' follow-up	Mild vitreous hemorrhage (6), nonresolving vitreous hemorrhage (4), one of them developed a scarred choroidal neovascular membrane, retinal detachment and massive subretinal bleeding (1), retinal tear (1)
NI	Best postoperative VA >20/200 in 10/24 (42%) (in 14 patients achieved by the first month of treatment)	11/24 (46%) 2 or more Snellen lines improvement, best postoperative VA	None
Total or subtotal in all eyes, not further specified	10/24 (42%) (mean 15.5, range 6–50 months' follow-up)	11/24 (46%) two or more Snellen lines improvement, final VA	Gas only: recurrent SMH (1), vitreous hemorrhage (7). rtPA IV: recurrent SMH (1)
Gas and rtPA: complete: 14/28 (50%), partial: 9/28 (32.1%), gas only: complete: 6/25 (24%), 7/25 (28%)	Gas and rtPA: 12/28 (43%) final VA (mean 12.8 months' follow-up, SD 0.96). Gas only: 3/25 (12%) final VA (mean 10.8 months' follow-up, SD 0.68)	Gas and rtPA: 17/28 (60.7%) improvement of 2 or more Snellen lines, best postoperative VA. Gas only: 8/25 (32%) 2 or more lines improvement	Gas and rtPA: vitreous hemorrhage (1), staphylococcal endophthalmitis (1), increased IOP (2). Gas only: vitreous hemorrhage (2), increased IOP (1)
13/14 (93%); 7/7 (100%)	4/7 (57%); 5/14 (36%), at 6 months	2 or more ETDRS lines improvement in 6/7 (86%) and 12/14 (86%) at 6 months	Recurrent submacular hemorrhage (2), in only gas group
NI	AMD 80%, RMA 84% (two methods taken together)	3 ETDRS lines or more: best PO VA: AMD: 76.9%, last visit AMD: 53.8%. RAM: 92.9% both best PO VA and last visit VA. Mean 18.4, range 3–61 months' follow-up	Not specified between groups: recurrent SMH (11), vitreous hemorrhage (3), increased IOP (5)
NI	NI	At 3 months without gas 2 or more Snellen lines improvement: 8%, with gas 25%. At 6 months without gas 13%, with gas 32%	Endophthalmitis (2), vitreous hemorrhage (10), subretinal hemorrhage (1), increased IOP (3)
9/11 (82%)	6/11 (55%), range 3–12 months' follow-up	Best PO VA: 2 or more Snellen lines improvement in 5/11 (45%), mean 4.8, range 3–12 months' follow-up	Exudative inferior retinal detachment (5), mild subretinal recurrent hemorrhage (1), vitreous haze (5), postoperative vitreous hemorrhage (5)
15/15 (100%)	6/15 (40%), range 4–19 months' follow-up	Best PO VA increased by 2 Snellen lines or more in 14/15 (93%) (average 4.6 months' follow-up). Final VA: 10/15 (67%), mean 10.5, range 4–19 months' follow-up	Breakthrough vitreous hemorrhage (3), endophthalmitis (1), recurrent hemorrhage (4)
22/22 (100%)	16/22 (73%)	No accurate information, only graph	Recurrent submacular hemorrhage (2), retinal detachment (1), vitreous hemorrhage (1), endophthalmitis (1)
45/53 (85%)	10/47 (21%) AMD, 4/6 (67%) RAM, mean 21 weeks' follow-up	AMD: 23/47 (49%) 2 Snellen lines or more improvement. RAM 5/6 (83%) 2 Snellen lines or more improvement. Mean of all patients 21 weeks' ($\pm$ 1 week) follow-up	Vitreous hemorrhage (4), endophthalmitis (1)
Complete: 1/8 (13%) after 1 week, 5/8 (also absorbed) (63%) at 6 months	3/8 (38%), at 6 months	3/8 (38%) 2 or more ETDRS lines improvement	IOP increase (1), bacterial endophthalmitis (1), vitreous hemorrhage (1)
10/11 (91%)	3/11 (27%)	1 week: 2 or more Snellen lines increase in 8/11 (72%), and 5/11 (45%) at 12 months	Recurrent submacular hemorrhage (2)
Complete: 10/14 (71%), partial: 3/14 (21%)	4/14 (29%), 1–15 months' follow-up	8/14 (57%) 2 or more Snellen lines improvement at 2 months. At last follow-up: 2/14 (13%) 2 or more Snellen lines improvement. Mean follow-up 7.7 months, range 1–15 months	Corneal edema (1), vitreous hemorrhage (1), posterior retinal tear within the superotemporal arcade (1), RPE tear (1)
35/43 (81%)	15/43 (35%), 4–18 months' follow-up	Best PO VA: 2 or more Snellen lines increase in 19/43 (44%). Final VA: 2 or more lines increase 13/43 (30%). Range 4–18 months' follow-up	Recurrent hemorrhage (9), mild breakthrough vitreous hemorrhage (3), IOP increased first postoperative day (2)
Complete: 21/25 (84%)	13/25 (52%) last VA, mean 7.1, range 4–18 months' follow-up	11/25 (44%) 2 or more Snellen lines, best PO VA. Mean best PO VA 4.7 months (range 0.5–12 months)	Recurrent subretinal hemorrhage (7), IOP increased first postoperative day (2)
NI	NI	Mean VA improvement/shift of 1.96 visual steps after 3 months' follow-up for the 47 patients tested at 3 months	5 patients underwent vitrectomy and subretinal surgery within 3 months, not further specified
Complete: 12/15 (80%), partial: 3/15 (20%)	Final VA 10/15 (67%) (mean 13 months, range 6–19)	7/15 (47%) 2 or more Snellen lines, best postoperative VA, mean 2.1 months (range 2 weeks to 4 months)	Breakthrough vitreous hemorrhage (2)
'Most cases'	11/19 (58%), mean 13 months, range 6–39 months' follow-up	Final VA: 2 or more ETDRS lines improvement in 12/19 (63.2%), 3 lines or more improvement in 10/19 (52.6%), mean 13 months' follow-up (range 6–39 months)	Breakthrough vitreous hemorrhage (3), retinal detachment (2), with unfavorable outcomes after multiple vitrectomies
63/85 (74%)	30/83 (36%), 12 months' follow-up	49/77 (63%) had a 2 Snellen lines improvement at 3 months, 52/81 (64%) at 12 months' follow-up	Breakthrough vitreous hemorrhage (8), retinal detachment (3)

(For table footnote see page 8.)

Table 1 (continued)

Reference	Number of eyes treated with rtPA	Etiology of hemorrhage	Vitrectomy	Tamponade	rtPA	Anti-VEGF
Kung, 2010 [40]	45	AMD (28), IPCV (11), RAM (2), pathologic myopia (3), trauma (1)	–	Gas (C3F8)	IV	–
Wu, 2011 [43]	120	AMD (88), IPCV (14), RAM (7), pathologic myopia (8), trauma (3)	–	Gas (C3F8); either the same day, or in case of elevated IOP after rtPA injection, 1 day after surgery	IV	–
Intravitreal rtPA and anti-VEGF agents and gas						
Meyer, 2008 [11]	19	AMD	–	Gas (SF6)	IV	IV during surgery (bevacizumab)
Sacu, 2009 [13]	20	AMD	–	Gas (SF6)	IV	IV (only in 3 eyes during same session as rtPA injection, 17 within 3 days after rtPA. On average: mean 1.6 injections during 4 months' follow-up)(16 bevacizumab, 4 ranibizumab)
Matt, 2010 [12]	10	AMD	–	Gas (SF6)	IV	IV (and at 4-week intervals after surgery if active CNV present or in case of persistent submacular hemorrhage) (ranibizumab)
Guthoff, 2011 [44]	38	AMD	–	Gas (SF6)	IV	IV (and at 4- or 8-week intervals after surgery according to CNV activity, in both groups) (during surgery bevacizumab, after surgery either ranibizumab or bevacizumab)
Mayer, 2011 [45]	32 (9 patients adverse events and left out of follow-up and therefore excluded)	AMD	–	Gas (SF6)	IV	4- to 6-week interval intravitreal injections in case of persistent sub-/intraretinal edema, new hemorrhage or active lesion (bevacizumab)
Vitrectomy, subretinal rtPA and air						
Olivier, 2004 [7]	29	AMD	Vitrectomy	Air	SR	–
Thompson, 2005 [9]	15	AMD	Vitrectomy	Air	SR	–
Singh, 2006 [8]	17	AMD	Vitrectomy	Air	SR	–
Sandhu, 2010 [46]	16	AMD	Vitrectomy	Air	SR	Only postoperative, IV (12). Mean number of injections at 6 months: 3.7, mean number at 12 months: 4.5 (ranibizumab)
Vitrectomy, subretinal rtPA and gas						
Hauptert, 2001 [5]	11	AMD	Vitrectomy	Gas SF6 (n = 8); air (n = 3)	SR	–
Fine, 2010 [47]	9 (with waiting period of 30–45 min; patients with retinotomy of 180–360° excluded)	AMD (massive SMH)	Vitrectomy	Gas (long-acting, not further specified)	SR	–
Hillenkamp, 2010 [6]	47	29 SR: AMD (26), RAM (2), trauma (1). 18 IV: AMD (15), RAM (3)	Vitrectomy	Gas (SF6)	SR (29); IV (18)	–
Vitrectomy, subretinal rtPA, intravitreal/subretinal anti-VEGF agent and gas						
Treumer, 2010* [48]	12	AMD	Vitrectomy	Gas (SF6)	SR	SR during surgery, IV 4 and 8 weeks after surgery (1 patient had an additional anti-VEGF injection during second rtPA application after SMH recurrence) (bevacizumab)
Arias, 2010 [10]	15	AMD	Vitrectomy	Gas (SF6)	SR (8); IV (7)	IV during surgery, bevacizumab. During follow-up 'as usual' (2 ranibizumab and 1 bevacizumab) in case of CNV activity in the rtPA IV group
Treumer, 2011 [14]	41	AMD	Vitrectomy	Gas (SF6)	SR	SR (bevacizumab SR during surgery and IV 4 and 8 weeks after surgery. Thereafter, flexible, predominantly visual acuity-driven treatment regimen with either bevacizumab or ranibizumab)
Rotterdam Eye Hospital, The Netherlands, 2012	28	AMD	Vitrectomy	Gas (SF6: n = 18; C3F8: n = 10)	SR	IV (n = 27 during surgery, bevacizumab and n = 27 after surgery, according to standard neovascular AMD treatment regimen of ranibizumab or bevacizumab)

Successful displacement (%)	Final VA >20/200 (%), follow-up	Eyes gained 2 (ETDRS or Snellen) lines or more (%), follow-up	Complications
Complete: 40/45 (89%), partial: 5/45 (11%)	18/45 (40%), 1–60 months' follow-up	Best PO VA: 2 or more Snellen lines improvement 21/45 (46.7%). Final VA 16/45 (36%) 2 or more lines. Mean follow-up 15.6 months, range 1–60	Breakthrough vitreous hemorrhage (9), 1 followed by macular pucker
NI	NI	Mean best postoperative VA: 5 ETDRS lines improvement (4.7 months). Mean final VA 2 Snellen lines improvement (22.6 months)	Breakthrough vitreous hemorrhage (18), retinal detachment (2)
17/19 (89%)	NI	Mean VA 2.1 lines ETDRS improvement at 1 month, 3.7 lines at 3 months' follow-up	Increased IOP or reduced retinal perfusion with therefore corneal paracentesis (12)
20/20 (100%)	Mean VA 0.27 ± 0.2, 4 months' follow-up	2 or more Snellen lines increase, 6/20 (30%), 4 months' follow-up	Vitreous hemorrhage (1)
10/10 (100%)	4/10 (40%)	Final VA: 7 eyes 1 Snellen line or more improvement (mean 6.4 months, range 3–13 months' follow-up)	Increased IOP (1), corneal erosion with IOP increase postoperative (1)
19/38 (50%)	NI	rtPA/gas: 3 Snellen lines or more improvement: 8/26 (31%), rtPA/gas/bevacizumab: 3 lines or more improvement: 5/12 (42%), both at 7 months' follow-up	No intra- or postsurgical complications
13/23 (56%)	10/23 (44%), 3 months' follow-up 14/21 (67%), 12 months' follow-up	12 letters (2.4 ETDRS lines) improvement, 6 months. 17 letters (3.4 ETDRS lines) improvement, 12 months' follow-up	Vitreous hemorrhages (10) of which 9 were excluded from analysis for that reason
Complete: 25/29 (86%), partial: 4/29 (14%)	12/29 (41%), range 3–6 months' follow-up	2 ETDRS lines or more gain in 17/29 (59%), 3 months' follow-up	Recurrent submacular hemorrhage (1), vitreous hemorrhage (2)
14/15 (93%)	NI	3/15 (20%) at 3 months 3 or more ETDRS lines improvement, 13% at 1 year 3 or more lines	Second vitrectomy for inadequate displacement of hemorrhage; removal of neovascular membrane/hemorrhagic complex surgically (1), recurrent submacular hemorrhage (1)
Complete: 9/17 (53%), partial: 8/17 (47%)	13/17 (76%) best postop VA >20/200 (3–48 months)	Improvement of VA, Snellen, (not further specified) in 12/17 patients (71%). Mean follow-up 17.2 months, range 3–48 months	Recurrent hemorrhage (3), retinal detachment (1)
Complete : 11/16 (69%), partial: 5/16 (31%)	NI (only graph)	10/16 (63%) 2 or more ETDRS lines improvement, at 6 months' follow-up, mean 3.4 lines	Recurrent SMH (2), one was mild and received anti-VEGF agent, the other, a major SMH, underwent SMH removal and RPE-patch procedure
11/11 (100%)	4/11 (36%) (1–15 months' follow-up)	Final VA: 2 ETDRS lines improvement in 6/11 (55%), mean 6.5, range 1–15 months' follow-up	Recurrent hemorrhage (3)
NI	2/9 (22%) (12 months' follow-up)	4/9 (44%) 2 or more ETDRS lines improvement, 12 months' follow-up	Retinal detachment (1), hyphema and/or vitreous hemorrhage (6), glaucoma (1)
IV: 4/18 (22%)/ SR: 16/29 (55%)	IV: 8/18 (44%), SR: 18/29 (62%), 1–3 months' follow-up, BCVA	IV: 8 improved -NI how many lines- (44%), SR: 19 improved -NI how many lines- (65%), Snellen. Final VA: 1–3 months' follow-up	IV: Vitreous hemorrhage (1), recurrent submacular hemorrhage (1). SR: Retinal detachment (3), vitreous hemorrhage (3; 1 associated with RD), recurrent submacular hemorrhage (2), RPE tear (1)
Complete: 9/12 (75%), incomplete: 3/12 (25%)	5/12 (42%), 12 weeks' follow-up	2 or more ETDRS lines improvement in 10/12 (83%), 12 weeks' follow-up	RPE tear due to inadvertent injection of rtPA and bevacizumab (1), secondary macular hole during subretinal injection (1), SMH recurrence (2)
Complete: 8/8 and 7/7 (100%)	SR: 0/8 (0%), IV: 2/7 (29%), 3–24 months' follow-up	Final VA: 2 ETDRS lines or more improvement in 7/8 (88%), 7/7 (100%), mean 11.8 months, range 3–24 months' follow-up	SR: RPE-tear (1), vitreous hemorrhage (3) IV: none
Complete: 35/41 (85%)	11/26 (42%), 12–32 months' follow-up	3 months: 30/41 (73%) 2 ETDRS lines or more improvement, final VA (12–32 months): 20/26 (77%)	RPE tear due to inadvertent injection of rtPA and bevacizumab (1), secondary macular hole during subretinal injection (1), retinal detachment (1), recurrence of SMH (8)
Complete: 16/28 (57%), partial: 11/28 (39%), none: 1/28 (4%)	11/28 (39%), 1–26 months' follow-up	14/28 (50%) at 1 month 3 or more ETDRS lines improvement. Final VA: 19/28 (68%) 3 or more lines improvement, range 1–26 months' follow-up	Macular hole (1), small pucker (2), recurrent submacular hemorrhage (2); in 1 causing retinal detachment, followed by PVR. Vitreous hemorrhage followed by recurrent retinal detachment and PVR (1), RPE tear (1), hyphema + hematocornea followed by vitreous hemorrhage (1)

(For table footnote see page 8.)

Group 1: no vitrectomy, intravitreal administration of rtPA, intravitreal injection of gas; group 2: no vitrectomy, intravitreal administration of rtPA and anti-VEGF agents, intravitreal injection of gas; group 3: vitrectomy, subretinal administration of rtPA, total gas or air tamponade; group 4: vitrectomy, subretinal administration of rtPA and either subretinal or intravitreal administration of anti-VEGF agents, total gas or air tamponade. As only complete hemorrhage displacement and major complications like retinal detachments were reported consistently, this study focuses on comparison of these data. Other variables of interest, such as preoperative VA, percentage of patients with a final VA >20/200, VA gain, partial displacement and complications other than retinal detachments, vitreous hemorrhages and/or recurrent submacular hemorrhages were too inconsistently described to allow comparison, and are therefore only displayed in the table. Two studies were excluded from comparison as they were earlier studies of later long-term studies and therefore used the same patients [39, 48]. Two other studies compared the intravitreal versus subretinal rtPA administration, both combined with vitrectomy and gas tamponade. Twenty-five patients who underwent vitrectomy and intravitreal rtPA administration in these two studies were not included in our analysis as they do not fit in either of the four groups, as they undergo vitrectomy (invasive) but the method of rtPA administration is intravitreal (minimal invasive) [6, 10].

The results of the less invasive method of rtPA administration (intravitreal rtPA; groups 1 and 2) were compared to those of the more invasive method (vitrectomy plus subretinal rtPA with gas or air; groups 3 and 4). The less invasive group had a range of 50–100% complete displacement rate (n = 467) [11–13, 24, 25, 29–35, 37, 38, 40, 42, 44, 45] while the most invasive group had a range of 53–100% displacement rate (n = 194, including 28 REH patients) [5–10, 14, 46]. The range of recurrence of submacular hemorrhage was 0–27% in both the less invasive and most invasive group. The range of retinal detachments was 0–45% in the less invasive group and 0–11% in the more invasive group. The percentage of vitreous hemorrhages ranged from 0–45% in the less invasive group

(n = 724) [11–13, 24, 25, 27–35, 37, 38, 40–45] and from 0 to 67% in the more invasive group (n = 203, including 28 REH patients) [5–10, 14, 46, 47] (table 2).

Comparison of the complications between groups 1 and 2 (intravitreal rtPA without (group 1; n = 607) or with (group 2; n = 117) anti-VEGF agents), revealed that in group 1, the percentage of recurrent submacular hemorrhage ranged from 0–27%. No studies in group 2 reported any cases of recurrent submacular hemorrhage. Vitreous hemorrhage rate ranged from 0–45% in group 1 [25, 27–35, 37, 38, 40–43], and 0–43% in group 2 [11–13, 24, 44, 45] (table 3).

Comparison of the complications between groups 3 (vitrectomy, subretinal rtPA, gas or air tamponade (n = 110)) [5–9, 47] and 4 (vitrectomy, subretinal rtPA and anti-VEGF agents with gas or air tamponade (n = 93, including 28 REH patients)) [10, 14, 46], revealed that in group 3, the rate of recurrent submacular hemorrhage ranged from 0–27 versus 0–20% in group 4. Vitreous hemorrhage rates ranged from 0–67% [5–9, 47], in group 3, to 0–38% [10, 14, 46] in group 4 (table 3).

Patients of the REH

At the REH, 28 patients with submacular hemorrhage due to AMD underwent vitrectomy, submacular rtPA injection and intravitreal gas injection between July 2008 and February 2011. The mean age was 83 years (SD ± 6.8); 18 patients were on systemic anticoagulation therapy before surgery, and 16 patients had received 1 or more intravitreal anti-VEGF injections at some point before surgery. Symptoms of the submacular hemorrhage had been present for a mean of 8.5 days (SD ± 6.3), with a range of 1–22 days. Seventeen eyes were pseudophakic before surgery, and 11 were phakic; 3 of the latter underwent phacoemulsification and implantation of an intraocular lens during their follow-up time. Median follow-up time was 6.5 months (range 1–26 months). Twenty-seven patients received an intravitreal anti-VEGF injection during surgery, and 27 (not the same) patients received a mean of 4 (range 1–15) anti-VEGF injections after surgery, according to standard treatment regimen for exudative AMD.

(Footnote from table 1.)

rtPA = Recombinant tissue plasminogen activator; anti-VEGF = anti-vascular endothelial growth factor; VA = visual acuity; RAM = retinal arterial macroaneurysm; AMD = age-related macular degeneration; NI = no (clear) information provided by the authors; BCVA = best-corrected visual acuity; ETDRS = early treatment diabetic retinopathy study; POHS = pre-

sumed ocular histoplasmosis syndrome; IPCV = idiopathic polypoidal choroidal vasculopathy; CNV = choroidal neovascularization; SR = subretinal; IV = intravitreal; IOP = intra-ocular pressure; RPE tear = retinal pigment epithelium tear; PVR = proliferative vitreo retinopathy. * Studies which included the same study patients in two reports.

Table 2. Comparison between minimally invasive and more invasive rtPA treatment methods

	Groups 1 and 2	Groups 3 and 4
Number	467	194
Complete displacement, %	50–100	53–100
Number	724	203
Recurrent submacular hemorrhage, %	0–27	0–27
Retinal detachment, %	0–45	0–11
Vitreous hemorrhage, %	0–45	0–67

Group 1: No vitrectomy, administration of rtPA intravitreally; group 2: no vitrectomy, administration of rtPA and anti-VEGF intravitreally; group 3: vitrectomy, administration of rtPA subretinally; group 4: vitrectomy, administration of rtPA subretinally, and anti-VEGF either subretinally or intravitreally. Anti-VEGF = Vascular endothelial growth factor inhibitors.

Table 3. Comparison between minimally invasive and more invasive rtPA treatment methods with or without additional anti-VEGF agents

	Group 1	Group 2	Group 3	Group 4
Number	350	117	101	93
Complete displacement, %	50–100	50–100	53–100	57–100
Number	607	117	110	93
Recurrent submacular hemorrhage, %	0–27	0	0–27	0–20
Vitreous hemorrhage, %	0–45	0–43	0–67	0–38

Group 1: No vitrectomy, administration of rtPA intravitreally; group 2: no vitrectomy, administration of rtPA and anti-VEGF intravitreally; group 3: vitrectomy, administration of rtPA subretinally; group 4: vitrectomy, administration of rtPA subretinally, and anti-VEGF either subretinally or intravitreally. Anti-VEGF = Vascular endothelial growth factor inhibitors.

The submacular hemorrhage was successfully displaced from the fovea in 16 patients (57%). In those patients in whom the hemorrhage was successfully displaced, the hemorrhage had been present for a mean of 8.1 days (SD $\pm$ 6.4). In 11 patients (39%), the hemorrhage was only partially displaced, and in 1 patient (4%), no displacement occurred. There was no relationship between the duration of hemorrhage and successful displacement.

Median preoperative best-corrected visual acuity (BCVA) was 1.8 logMAR (range 0.3–2.8). The BCVA improved significantly to a median BCVA of 1.2 (range 0.35–2.8) at 1 month postoperatively. Median BCVA at the last follow-up visit further improved 1.14 logMAR (range 0.15–2.1). The best median BCVA was found at a median of 2 months postoperatively (range 0.5–13 months). This best median BCVA was 0.8 logMAR (range 0.1–2.3).

At 1 month after surgery 14/28 (50%) of the patients had improved 2 or more ETDRS lines. At the last follow-

up visit, 19/28 (68%) had improved 2 or more ETDRS lines as compared to preoperative baseline BCVA.

Complications in the Patients of the REH

Eight of the 28 patients experienced complications after surgery. Two patients experienced a recurrent hemorrhage. One patient developed a macular hole. One patient developed an RPE-tear after several anti-VEGF injections. Two patients developed a small macular pucker without further treatment. One patient developed a vitreous hemorrhage. One patient developed a hyphema with hematocornea, followed by a vitreous hemorrhage.

Of these 8 patients who experienced complications, 2 developed PVR. One of the patients with a recurrent submacular hemorrhage had subsequently a retinal detachment followed by PVR. The other patient was the one who developed a vitreous hemorrhage first; which was followed by a retinal detachment, subsequently followed by PVR.

Discussion

Review of Case Series

There were several obvious difficulties in comparing the results of these 38 reports. Because all 38 reports were case series with varying sizes and protocols, there was no consistent, uniform definition or reporting of the size of the hemorrhage, initial visual acuity, time between hemorrhage and treatment, total or partial displacement of the hemorrhage, VA gain or loss, or complications. Therefore, comparisons could not be statistically analyzed, and can thus only be descriptive. It was determined that it would be most useful to describe only four groups of studies. Additionally, only the rates of the hemorrhage displacement and the major complications of vitreous hemorrhage, retinal detachment and recurrent submacular hemorrhage were compared, as only these data were retrievable in a majority (32 of 38) of the studies.

Because of these limitations, it was not possible to perform a meta-analysis and to draw firm conclusions. However, it was noted that a 100% displacement rate could be achieved in both the less invasive (injections only) and the more invasive (vitrectomy) groups. Further, complication rates were relatively consistent between groups. It is notable that no recurrent submacular hemorrhages were reported in any of the studies with intravitreal rtPA plus anti-VEGF agent [11–13, 44, 45]. Whether this was because the anti-VEGF agent helped to prevent the recurrence of submacular hemorrhage or because the recurrent submacular hemorrhages were not reported as a complication, but rather a retreatment criterion, is unclear. However, this difference is not clearly seen when vitrectomy was used in combination with anti-VEGF. Without recurrent submacular hemorrhage and treatment of choroidal neovascularization more VA gain might then also be likely, but such conclusions could not be drawn from the available data.

There are several considerations on the safe and effective use of rtPA and anti-VEGF. Regarding rtPA: Retinal penetration of the molecule, its potential toxicity and the best possible timing of its administration, both in terms of survival of the overlying retina and the ability to lyse the clotted blood. Regarding the anti-VEGF: The potential side-effects of anti-VEGF agents and its potential interaction with rtPA.

Liquefaction and Diffusion Capacities of rtPA

rtPA is a thrombolytic agent that activates plasminogen into plasmin, which has the ability to enzymatically liquefy recent hemorrhage via lysis of the fibrin. In the

context of a submacular hemorrhage, this fibrin is located between the photoreceptors. Lysis of the fibrin allows for the detachment of the hemorrhage from the outer retina and RPE and its relocation, thereby minimizing shearing damage to the outer segments of the photoreceptors. The rtPA action is believed to be rapid in onset, within minutes. However, this action requires direct contact with fibrin [49].

rtPA has a molecular weight of 70 kDa which prevents its diffusion across intact biological membranes [50]. This includes retina, as the pore size of the outer limiting membrane is between 30 and 36 Å, corresponding to molecules around 50–60 kDa [49, 51]. However, although rtPA theoretically should not diffuse through the retina, Kamei et al. [52] demonstrated a signal of rtPA in the neural retina in some rabbit eyes, which they hypothesize to be due to microscopic retinal tears secondary to the subretinal hemorrhage. This might be the reason that rtPA seems to diffuse into the subretinal space in AMD patients with SMH.

Toxicity of rtPA

rtPA might be toxic to the RPE and retina, and this has been studied in rabbits and cats [53, 54]. In a tolerance study, a concentration of 20 µg/ml was found to be safe for the treatment of SMH, in combination with 0.25 mg/ml bevacizumab [55], Hesse et al. [33] suspect a toxic effect on the retina when 100 µg is given intravitreally, as all patients treated with 100 µg experienced exudative inferior retinal detachments, while no complications were found in the patients who received 50 µg. A case report described toxicity with 50 µg/ml rtPA [56]. In other studies, doses up to 100 µg have been given with good outcomes and without side effects due to toxicity [29, 31, 44]. In other reports, functional improvement in the majority of patients which mainly received up to 50 µg/0.1 ml rtPA, suggests the absence of direct retinal toxicity at this concentration of rtPA, administered either subretinally [5, 6, 48] or intravitreally [6, 11, 32, 36]. Based on previous reports' conclusions, namely: equal efficacy over the range of 25–100 µg intravitreally [31] the possibility of toxicity at doses of 50 µg or higher [33, 56], and the lack of adverse events reported in the toxicity tolerance study in which a concentration of 20 µg/ml was applied subretinally in combination with 0.25 mg/ml bevacizumab [55], we conclude that a dose of 25 µg/0.1 ml of rtPA, either administered subretinally or intravitreally, either alone or in combination with a 0.25 mg/ml concentration of bevacizumab administered intravitreally seems likely to be a safe and effective concentration.

Toxicity of Anti-VEGF

Clinical and dose-relation studies have not shown any direct retinal toxicity due to the standard dose of 1.25 mg/0.05 ml bevacizumab or 0.50 mg/0.05 ml ranibizumab. Further, no signs of toxicity were found in safety studies of intravitreal injections in rabbit [57–59], murine [60] or bovine [55] models. Indeed, no difference in ERG parameters was found in mouse retina after the application of 1.0 µl of a 25-mg/ml solution of bevacizumab [60]. A retinal tolerance study of intravitreal injections of bevacizumab in combination with rtPA application in bovine eyes found that a concentration of 0.25 mg/ml (equivalent to 1.25 mg per human eye) was safe, even when combined with the administration of 20 µg/ml rtPA [55]. Most convincingly, several clinical studies involved the administration of standard doses (up to 1.5 mg avastin) into the posterior segment after partial or total gas tamponade [10, 44]. Given the small fluid phase left in such eyes, a high concentration of anti-VEGF might be reached. However, no toxicity was reported [10, 44]. Indeed, Treumer et al. [14, 48] injected 1.25 mg/0.05 ml bevacizumab subretinally, which might be expected to result in considerably higher concentrations. Also here, no apparent toxicity was noted.

Effectiveness of Anti-VEGF

Severe closure of normal capillaries has been demonstrated after intravitreal injection of 1.25 mg/0.05 ml bevacizumab. When patients with severe CNV are treated with bevacizumab, ischemia of retinal capillaries and choroidal atrophy might occur [61]. However, injections with anti-VEGF have become standard treatment of exudative AMD, because of their effectiveness in treating choroidal neovascularization [62, 63]. Nevertheless, certain patient groups do not respond well to anti-VEGF therapy, among whom patients with a large hemorrhage [64]. Other patients may exhibit overexpression of TNF-α. This overexpression of TNF-α reduces the expression of FcRN, the receptor responsible for immunoglobulin transmembrane transport. Because the ocular pharmacology of anti-VEGF agents seems to depend on the expression of FcRN, some patients with a large CNV membrane due to AMD might have a low level of FcRN expression, and might therefore derive little therapeutic benefit from anti-VEGF agents [65].

Subretinal rtPA and bevacizumab can be co-applied; no cleavage or functional inactivation of bevacizumab by rtPA was found in vitro, and significant VA improvement in the short and long term were observed in vivo [14, 66].

Toxicity of a Hemorrhage and Time Frame for Removal of a Hemorrhage

Damage to the sensory retinal tissue due to SMH is caused by a limitation of nutrient passage to the retina, shrinkage of the outer retinal layers due to clot formation [67] and the release of retinotoxic substances such as fibrin [3], iron [68, 69] and hemosiderin [70]. Toxic effects of the SMH can be observed as early as 24 h after the hemorrhage [67]. Later, the resolution of the hemorrhage is followed by the formation of a macular scar or fibrous tissue proliferation [71]. The prognosis of large, untreated subretinal hemorrhages is very poor [16, 17]. Animal models have shown progressive, irreversible degeneration of the outer retina and RPE. As early as 1 day after the initiation of the hemorrhage, damage of the photoreceptor cells, characterized by edema and disintegration of the photoreceptors is observed [67]. At 7 days, significant destruction of the outer retinal elements is seen, as well as severe degeneration, or even absence of photoreceptor outer and inner segments [3, 67]. The RPE cells show shortened apical microvilli, and distortion of mitochondria [3]. At 14 days, extensive and severe destruction of the outer retinal layers is found [2, 3], photoreceptor damage and increasing numbers of phagocytic cells immediately overlying the RPE layer are observed. Atrophy and disorganization of the outer retinal layers, with proliferation of fibrolytic cells, occurs in the most severely damaged areas of the retina. The inner retinal layer shows severe vacuolization. In the RPE, vacuoles can be observed, along with disorganization of the cytoplasm. The progressive, focally severe injury of the retina seems to occur between 7 and 14 days after hemorrhage [3]. It has been reported that if SMH is removed the latest at day 7 after the initial hemorrhage, retinal architectural integrity is better maintained [2].

Time Window of Liquefaction of rtPA

Several clinical studies have been performed to investigate the importance of the interval between the initiation of hemorrhage and the surgical treatment. An rtPA-assisted surgical drainage pilot study showed that subretinal blood liquefied in 88% of the cases when injected within seven days or less, while only 37.5% demonstrated blood liquefaction if the SMH had existed for 8–14 days [72]. VA improved in all 16 eyes with a SMH of 7 days or less, with half of them having a VA of 20/200 or better, while VA improved in only half of the patients with a hemorrhage of eight to 14 days, and none of these patients achieved a 20/200 VA postoperatively [72].

Morse et al. [73] injected rtPA in 4-day-old SMH. They did not find therapeutic benefit from the rtPA injection without surgical removal of the hemorrhage in a cat model. Moreover, they found a second focus of retinal degeneration at a gravity-dependent inferior site to which the blood had migrated. Hesse et al. [33] treated 11 patients with intravitreal rtPA, followed by a gas tamponade. Nine were treated between 12 and 72 h of the hemorrhage; 2 were treated more than 14 days after the hemorrhage occurred. There was a clear advantage in those treated early as compared to those treated late. Hattenbach et al. [32], who also treated with intravitreal rtPA and gas tamponade, showed that eyes with symptoms less than 14 days' duration seem to benefit most. Indeed, VA improved 2 or more Snellen lines in 67%, as compared with only 29% of eyes with duration of >14 days.

It thus appears to be best to treat patients within 14 days after the initiation of the hemorrhage, because liquefaction and displacement of the clot is most likely; moreover, irreversible retinal damage occurs after that period.

Conclusions

Intravitreal rtPA application with an intravitreal gas injection only, or subretinal rtPA application with vitrectomy and gas tamponade, can achieve successful displacement of a recent submacular hemorrhage, frequently resulting in improvement of VA. Our review of available clinical reports suggests that intravitreal rtPA and gas, without vitrectomy, might be as effective as submac-

ular rtPA with vitrectomy, while most likely being associated with fewer complications. Nevertheless, recent reports tend to favor the use of vitrectomy. Additional intra- or postoperative anti-VEGF treatment shortly after surgery might help prevent recurrent submacular hemorrhage. Also, it is likely that treatment within 2 weeks is most effective in displacing blood and increasing the chances of long-term improvement of visual acuity.

A prospective, randomized study is needed in order to investigate how the combination of intravitreal rtPA, intravitreal bevacizumab and gas tamponade of the posterior segment, without vitrectomy, compares with the combination of vitrectomy, subretinal injection of rtPA, gas tamponade and intravitreal injection of bevacizumab, in terms of safety and efficacy.

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