EXTENDED REPORT

Comparison of a non-preserved 0.1% T-Gel eye gel (single dose unit) with a preserved 0.1% T-Gel eye gel (multidose) in ocular hypertension and glaucomatous patients

D L Easty, G Nemeth-Wasmer, J-P Vounatsos, B Girard, N Besnainou, P Pouliquen, L Delval, J-F Rouland

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See end of article for authors' affiliations

Correspondence to: Professor David L Easty, Department of Ophthalmology, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX, UK; david.easty@bristol.ac.uk

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Aim: This comparative, open design, phase III study was to assess the non-inferiority of the non-preserved T-Gel 0.1% single dose unit (SDU) versus its preserved multidose (MD) reference.

Methods: 175 patients with bilateral POAG or OHT were randomised: 87 patients were to receive one drop daily of T-Gel 0.1% MD and 88 patients were to receive one drop daily of T-Gel 0.1% SDU, for a treatment period of 12 weeks. The primary efficacy variable was the change in intraocular pressure (IOP) in the worse eye between the baseline and the last assessment. Subjective and objective ocular signs as well as adverse events were recorded for safety. Global tolerance was assessed by the investigator and by the patient.

Results: The mean percentage reduction from baseline IOP was 24% for both treatments groups, which was consistent with previous studies. The safety results were comparable in both treatment groups. Because of gel formulation, mild short lasting episodes of blurred vision occurred for about 20% of patients. The global tolerance assessment reported that both treatments were well tolerated.

Conclusion: The overall study results demonstrated that T-Gel 0.1% SDU is not inferior to T-Gel 0.1% MD.

In patients with primary open angle glaucoma (POAG) and ocular hypertension (OHT), the only approach presently proved to be efficient in preserving visual function is to lower the IOP.[1] Currently, β blockers are used as one of the first choices of therapy as they are known to be effective and usually well tolerated since their introduction in 1978.[1]

New low dosage gel formulations have been designed in order to reduce the drug exposure.[2–12] In particular, improved bioavailability by carbomer gels[13] results in reducing the frequency of instillations and the timolol product concentration. In a previous prospective multicentre study, Rouland *et al*[10] demonstrated that Nyogel 0.1%, a novel carbomer formulation of low dosage timolol 0.1% in a hydrogel vehicle, instilled once daily, was equally effective to conventional timolol 0.5% solution instilled twice a day. The fivefold dose reduction and the twofold frequency of instillations reduction result in a 10-fold timolol concentration lowering, thus significantly reducing the likelihood of systemic side effects. In a comparative safety study, Niño *et al*[8] showed that the cardiovascular effects of timolol 0.1% hydrogel are comparable with placebo effects, whereas aqueous 0.5% timolol ophthalmic solution may induce some cardiovascular β blocking effects.

Furthermore, the toxic action of preservatives on the ocular surface has been widely demonstrated[14 15] and various studies suggested that the topical side effects occurring are partly resulting from the presence of preservatives.[16–19] Benzalkonium chloride (BAK), a quaternary ammonium, is the most commonly used preservative in multidose ophthalmic preparations to limit bacterial contamination. However, BAK is known to decrease the stability of the precorneal tear film and its toxic and inflammatory action on the ocular surface is accentuated by the cumulative effect of repeated instillations of preserved eye drops.[17] In addition, the toxicity of preserved eye drops is strongly suspected to impair the efficacy of subsequent surgery.[19–21] In glaucoma requiring a long term antiglaucomatous treatment, the development of preservative free gel formulated eye drops therefore constitutes a real healthcare concern.

The aim of this study was to compare the efficacy and safety of a low dosage timolol formulation with and without preservative: non-preserved T-Gel 0.1% single dose unit (SDU) was compared to its reference and marketed BAK preserved T-Gel 0.1% multidose (MD).

MATERIAL AND METHODS

Patients

A total of 175 patients were randomised among 53 centres in France and one in Portugal. Eligible patients had to present bilateral POAG or OHT likely to be controlled by a β blocker monotherapy: IOP $\geqslant$21 mm Hg in one eye and IOP $<$31 mm Hg in both eyes, without treatment. Exclusion criteria were as follows: any severe glaucoma, best visual acuity (VA) $\leqslant$20/200, ocular allergy, procedures for glaucoma within the previous year before the study, trauma, infection or inflammation within 3 months before the study; other relevant abnormalities, contact lenses, pregnancy, lactation and pre-menopausal women not on reliable birth control, contraindications for β blockers, or any alteration in dose regimen of treatment which could interfere on IOP. All the subjects signed written informed consent. The study was approved by an independent ethics committee and was conducted in compliance with ethical principles of the Declaration of Helsinki.

Study design

After a 3 week run in period, all the patients underwent IOP measurements with a Goldmann applanation tonometer at day 0 (the inclusion visit). At H0 (before instillations), all

Abbreviations: AEs, adverse events; BAK, benzalkonium chloride; BUT, break up time; IOP, intraocular pressure; LOQ, lower limit of quantification; MD, multidose; OHT, ocular hypertension; POAG, primary open angle glaucoma; SDU, single dose unit; VA, visual acuity

eligible patients underwent an ocular examination including best distance corrected VA, subjective ocular signs, slit lamp examination of the anterior segment with fluorescein stain, and recording of adverse events (AEs) under previous treatment. All eligible patients were then randomly allocated to one of the two study medication groups: T-Gel 0.1% SDU (non-preserved eye gel, Geltim/Timogel from Laboratoires Thea) or T-Gel 0.1% MD (preserved eye gel, Timogel from Laboratorios Thea). The study had an open design since single dose containers (T-Gel 0.1% SDU) and multidose vials (T-Gel 0.1% MD) could not be masked. However, the main criterion was the IOP measurement, which is an objective variable. Patients were to receive one drop of the study medication into the lower conjunctival sac of each eye once daily in the morning for a 12 week period. Patients attended two follow up visits: week 4 and week 12, or at a final visit (last assessment) when week 12 was not accomplished. At the 12 week visits, IOP measurement was made before instillation of the study medication (H0) and 2 hours after instillations (H2).

Efficacy

The primary efficacy variable was the change in IOP in the worse eye between baseline (day 0, H0) and the assessment before instillation at the last attended visit after baseline (''last assessment,'' H0). The worse eye was defined as the eye with the higher IOP at baseline.

The secondary efficacy variables were as follows: change in IOP between baseline and day 0 (H2), at week 4 (H0) and at the last assessment (H2); global efficacy by the investigator; number of withdrawals for therapeutic failure.

Safety

Safety and tolerance were assessed using the following variables: subjective expected ocular signs upon instillation (irritation/burning/stinging, eye dryness, foreign body sensation, blurred vision); objective ocular signs (slit lamp examination including palpebral abnormality, conjunctival hyperaemia, folliculo-papillary conjunctivitis, corneal staining punctuations, anterior chamber flare, other abnormalities); global local tolerance (by investigator and patients); best corrected VA, ocular and systemic AEs. Additionally, timolol plasma levels were to be analysed in approximately 20 patients at week 12 (at H0 and H2). The analysis was performed using high performance liquid chromatography coupled with mass spectroscopy (lower limit of quantification (LOQ) = 0.8 ng/ml).

Statistical evaluation

The principal statistical hypothesis was that T-Gel 0.1% SDU was not inferior to T-Gel 0.1% MD. The evaluation was performed by calculating the two sided 95% confidence intervals (CIs) on the difference between the two treatments, and comparing its upper limit with the non-inferiority margin (1.5 mm Hg). This CI was obtained using analysis of variance (ANOVA) and was controlled by the baseline IOP. Factors for the analysis of variance were: treatment, centre, and treatment by centre interaction.

The quantitative variables recorded at onset of the study are compared in the two treatment groups using the independent *t* test, the ordinal variables using the Mann-Whitney test and the binary variables using the Fisher's exact test.

The sample size determination

A requirement for 63 patients in each treatment group was calculated using an alpha risk of 5%, a beta risk of 20%, and an estimated standard deviation (SD) of 3.0 mm Hg.

The sample size for timolol pharmacokinetics was chosen in accordance with recent published data on a similar study.[10]

RESULTS

Out of the 175 randomised patients, 10 patients discontinued the study prematurely and 19 presented major protocol deviations, mainly poor compliance and non-respect of inclusion criteria. Thus, the per protocol (PP) population consisted of 146 patients: 72 in the T-Gel 0.1% MD group and 74 in the T-Gel 0.1% SDU group.

The mean age of the patients was 61.5 (SD 11.2) years and the proportion of females (56.0%) was higher than males (44.0%). There were no significant differences between the two treatment groups with respect to age ($p = 0.738$; *t* test), sex ($p = 0.880$; Fisher's exact test). Before the study, 81 patients (55.5%) were treated with an anti-glaucomatous product (β blocker monotherapy) and 65 patients (44.5%) were not treated. There were no notable differences between the treatment groups regarding pretreatment status. At baseline, IOP values were similar for both treatment groups (table 1).

Table 1 Mean IOP values (mm Hg) during the study (PP population)

	T-Gel 0.1% MD	T-Gel 0.1% SDU			
Review period	Mean (SD) (n = 72)	Mean (SD) (n = 74)	Mean difference	Two sided 95% CIs on mean difference	Non-inferiority
Baseline, H0	23.51 (1.75)	23.76 (1.98)			
Baseline, H2	17.97 (2.95)	18.07 (3.25)			
Change†	5.54 (2.93)	5.69 (3.51)	−0.15	(−0.90; 0.60)	Accepted
Mean reduction (%)	23.42 (11.76)	23.65 (13.85)			
Week 4, H0	17.63 (2.48)	17.61 (2.46)			
Change†	5.88 (2.69)	6.15 (2.58)	−0.27	(−0.88; 0.34)	Accepted
Mean reduction (%)	24.77 (10.80)	25.65 (10.20)			
Week 12, H0	17.88 (2.88)	18.13 (2.73)			
Change†	5.63 (2.93)	5.63 (2.76)	0.00	(−0.66; 0.66)	Accepted
Mean reduction (%)	23.78 (12.00)	23.50 (11.07)			
Week 12, H2*	16.09 (2.74)	16.28 (2.63)			
Change†	7.42 (2.92)	7.48 (2.55)	−0.07	(−0.72; 0.58)	Accepted
Mean reduction (%)	31.36 (11.75)	31.39 (10.06)			
Last assessment, H0	17.88 (2.88)	18.13 (2.73)			
Change†	5.63 (2.93)	5.63 (2.76)	0.00	(−0.66; 0.66)	Accepted
Mean reduction (%)	23.78 (12.00)	23.50 (11.07)			

*One missing datum in the T-Gel 0.1% MD group.
†Change in comparison with baseline H0.

Table 2 Expected subjective ocular signs upon instillation (safety population)

		T-Gel 0.1% MD (n = 87)			T-Gel 0.1% SDU (n = 88)		
			Absence	Presence		Absence	Presence
Sign	Visit	No	No (%)	No (%)	No	No (%)	No (%)
Irritation/burning/stinging	Baseline, H0*	87	82 (94.25)	5 (5.75)	88	84 (95.45)	4 (4.55)
	Week 4	84	76 (90.48)	8 (9.52)	86	79 (91.86)	7 (8.14)
	Week 12	86	76 (88.37)	10 (11.63)	86	81 (94.19)	5 (5.81)
Eye dryness	Baseline, H0*	87	86 (98.85)	1 (1.15)	88	86 (97.73)	2 (2.27)
	Week 4	84	84 (100.0)	–	86	80 (93.02)	6 (6.98)
	Week 12	86	82 (95.35)	4 (4.65)	86	81 (94.19)	5 (5.81)
Foreign body sensation	Baseline, H0*	87	86 (98.85)	1 (1.15)	88	84 (95.45)	4 (4.55)
	Week 4	84	80 (95.24)	4 (4.76)	86	80 (93.02)	6 (6.98)
	Week 12	86	84 (97.67)	2 (2.33)	86	82 (95.35)	4 (4.65)
Blurred vision	Baseline, H0*	87	87 (100.0)	–	88	87 (98.86)	1 (1.14)
	Week 4	84	75 (89.29)	9 (10.71)	86	74 (86.05)	12 (13.95)
	Week 12	86	75 (87.21)	11 (12.79)	86	77 (89.53)	9 (10.47)

*After the run-in period (no treatment), some patients presented spontaneously subjective ocular signs.

Efficacy variables

In the PP population, the mean reduction was 5.63 (2.93) mm Hg in the T-Gel 0.1% MD group and 5.63 (2.76) mm Hg in the T-Gel 0.1% SDU group (table 1) at the last assessment (corresponding to week 12). The mean percentage reduction from baseline IOP in each treatment group was 24%. T-Gel 0.1% SDU was demonstrated to be non-inferior to T-Gel 0.1% MD for the primary efficacy variable: the upper limit of the two sided 95% CIs on the mean difference was 0.66 and did not exceed the non-inferiority limit of 1.5 mm Hg.

In both treatment groups, the mean percentage reduction IOP at week 4 and week 12 was about 25%. Non-inferiority of T-Gel 0.1% SDU versus T-Gel 0.1% MD was confirmed (table 1). As expected, the mean IOP reduction 2 hours after instillation was greater at week 12: 31% in both treatment groups. Non-inferiority of T-Gel 0.1% SDU versus its reference product was confirmed once again (table 1).

The investigator assessed the global efficacy of both treatments as ''very satisfactory'' or ''satisfactory'' for about 92%. Moreover, no patient in either treatment group was considered to have been withdrawn from the study because of therapeutic failure.

Safety

The safety population consisted of all randomised patients who received at least one dose of the study medication. Thus, all 175 patients were included, 87 in the T-Gel 0.1% MD group and 88 in the T-Gel 0.1% SDU group. Only four patients presented ocular AEs considered to be treatment related, one in the T-Gel 0.1% MD group (blurred vision) and three in the T-Gel 0.1% SDU group (one with eye irritation and two with lacrimal disorders). Only eight patients presented systemic AEs considered to be treatment related: five in the T-Gel 0.1% MD group (one with abdominal upper pain, one with dry mouth, one with osteoarthritis, one with nightmares, and one with erectile dysfunction), while three in the T-gel 0.1% SDU group (one dyspnoea, one dermatosis, and one erectile dysfunction). All these AEs were reported as mild to moderate in intensity.

In both treatment groups, some patients presented spontaneously at baseline with symptoms of irritation, burning, stinging, and/or eye dryness, and/or foreign body sensation, while not under treatment (table 2).

A slight increase in these signs was observed upon instillation during the study. Most of the cases were not clinically significant and of short duration. After 3 months of treatment, the frequency of irritations/burning/stinging upon instillation were reported to be twice as high in the T-Gel 0.1% MD group than the T-Gel 0.1% SDU group. In addition, the occurrence of the symptoms at week 12 in the T-Gel 0.1% MD group was higher than that observed at day 1, while they did not increase in the T-Gel 0.1% SDU group during the study. These trends in favour of a better local tolerance in the T-Gel 0.1% SDU group upon instillation were not statistically significant. Blurred vision upon instillation was reported for approximately 10% of patients in each treatment group whereas this symptom was barely present at baseline (table 2). This result is to be expected when spreading a gel on the ocular surface. However, the majority of these episodes were of short duration. Neither of the study medications had any notable effect on the ocular signs assessed in the slit lamp examination and fluorescein staining.

The global tolerance assessments were very similar in both treatment groups: treatments were considered as well tolerated by more than 95% of the patients; and as ''very satisfactory'' or ''satisfactory'' by approximately 95% of the investigators.

Plasma timolol levels were measured in 27 patients in the ITT population. Once daily topical ocular instillations of T-Gel 0.1% MD or SDU eye gels predominantly did not result in quantifiable levels of timolol in the plasma, except for one patient in each treatment group.

DISCUSSION

T-Gel 0.1% SDU contained a gel of Carbomer 974P with polyvinyl alcohol known to increase bioavailability, resulting in the reduction of the frequency of instillation and of the timolol concentration.[22] In our clinical trial, the reference formulation T-Gel 0.1% MD was identical, with BAK as a preservative.

Analysis of the primary efficacy variable reported a mean IOP reduction of about 24% for both formulations. This IOP lowering effect was of the magnitude to be expected with topically applied timolol 0.1% hydrogels.[2–5 7 9 10 23] Moreover, the mean IOP reduction of 31% after 2 hours confirms these results.[7 10] Other studies previously showed that this low dosage formulation instilled once daily is as efficient as conventional aqueous timolol formulations.[2–7 9 10 24] The morning instillation allows the efficacy peak during the first period of the day, which corresponds to the time of the IOP peak observed in most glaucomatous patients.[25–27] Additionally, once daily instillation is expected to improve treatment compliance.[10]

BAK has a potential role as an enhancer for intraocular penetration of the active ingredients. It is closely linked to its well known toxicity on the ocular surface. Indeed, BAK is a detergent agent, able to impair the corneal epithelium, which

represents the main barrier to intraocular penetration. When exposed to BAK, particularly in dry eye patients,[28] corneal permeability can dramatically increase. The effect of penetration enhancer has been suggested to increase the amount of active product available in the anterior chamber and to enhance the product efficacy. Such a hypothesis is not confirmed by our results. The efficacy of non-preserved T-Gel 0.1% SDU is not inferior to BAK preserved T-Gel 0.1% MD. Our results are consistent with all published clinical trials, none of which showed differences in efficacy[16 17 29] between the preserved and the non-preserved formulations.

Global assessment judged both medications well tolerated by the patient and the investigator. The main symptom upon instillation was blurred vision, usually lasting a few minutes which is an expected ocular symptom of timolol in a gel.[6] Regarding ocular and systemic AEs, only a few were reported as being treatment related and they were all of mild to moderate intensity.

Overall, the safety profile is similar in both treatment groups for three reasons. First of all, good tolerance results have already been observed when applying a low dosage BAK preserved formulation. Ardjomand *et al*[3] showed an increased lacrimal production (Schirmer's test) as well as an increased break up time (BUT) values after 3 months of treatment with timolol maleate hydrogel 0.1%. Secondly, the duration of this once daily product instillation study is probably too short to highlight a potential dose related toxicity of BAK. Finally, methodology designs for phase III studies are not as accurate as for studies aimed to detect slight differences between groups. In such studies, the occurrence of ocular signs was shown to be lower in the non-preserved T-Gel 0.1% SDU group. In a comparative study between BAK preserved and non-preserved carteolol treatments in healthy subjects, Baudouin *et al*[30] showed that exposure to preserved carteolol resulted in a reduction of BUT confirming a better tear film stability in the non-preserved treatment group. Similarly, two comparative studies between BAK preserved and non-preserved timolol treatments reported an increased tear film instability as a result of preservative. Ishibashi *et al*[31] (timoptol versus Timabak in healthy subjects) showed that exposure to BAK preserved timolol resulted in a significant reduction of the non-invasive BUT and Manni *et al*[17] (Timoptol versus Timolabak in glaucomatous patients) showed a reduction of BUT and an increased expression of interleukin 1β inflammatory marker after exposure to BAK preserved timolol. Furthermore, the preservative toxicity has also been confirmed by long term epidemiological studies: Baudouin *et al*[32] confirmed the increased expression of inflammatory markers in glaucomatous patients under preserved β blocker treatments; Pisella *et al*[18] described a lower prevalence of symptoms and signs after instillation of non-preserved eye drops.

Regarding side effects, the safety profile in our study was very satisfactory. A recent review[33] of the relevant articles published from 1966 to 2002 identified no scientific studies supporting the development of worsening claudication, depression, hypoglycaemia, unpaired neuromuscular transmission, or sexual dysfunction with systemic or ophthalmic β blockers. In particular, a recent study[34] suggested that the knowledge and prejudice about side effects of β blockers could produce anxiety that might further cause the occurrence of erectile dysfunction, which is reversed by placebo. Nevertheless, bronchial hyper-reactivity or cardiac conduction defects remain actual contraindications to ophthalmic β blockers. As stated by Lama,[33] a careful medical history and checks of pulse rate and rhythm allow identification of patients with potential cardiac contraindications, who will seek medical help from a cardiologist. Patients who have had successful pacemaker implantation may be safely prescribed an ophthalmic β adrenergic blocker. However, patients with bronchial hyper-reactivity should not be prescribed these drugs

Pharmacokinetic assessments reported in our study are in correlation with published data showing low systemic exposure with low dosing 0.1% timolol formulation. Data on the C_{max} and the area under the curve values of timolol plasma are 10-fold lower in the timolol 0.1% gel than timolol 0.5%.[11] This significant difference in the plasma concentrations of timolol confirms that a low dosage formulation is expected to reduce the incidence of systemic AEs.

CONCLUSION

As expected, non-preserved T-Gel 0.1% SDU efficacy is not inferior to preserved T-Gel 0.1% MD, confirming the hypothesis that the preservative does not interfere with the efficacy of the product. Even if the occurrence of side effects was equivalent in both treatment groups, this would be expected to be minimised within the non-preserved treatment group after a longer treatment period. Owing to its low dosage and preservative free formulation T-Gel 0.1% SDU can be therefore considered as a first line treatment in the prescription of the β blocker class of drugs.

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Authors' affiliations

D Easty, Department of Ophthalmology, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX, UK
G Nemeth-Wasmer, 5 place du 2 Février, 68000 Colmar, France
J-P Vounatsos, 30 cours de l'Intendance, 33000 Bordeaux, France
B Girard, 41 rue de Liège, 75008 Paris, France
N Besnainou, 9 avenue de la République, 94700 Maisons Alfort, France
P Pouliquen, L Delval, Laboratoires THEA, 12 rue Louis-Blériot, ZI du Brézet, 63017 Clermont-Ferrand Cedex 2, France
J-F Rouland, Hôpital Huriez, Aile Ouest, Service d'Ophtalmologie, Place de Verdun, 59000 Lille, France

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