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Atosiban versus usual care for the management of preterm labor

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Abstract

Objective: To compare the efficacy of atosiban with usual management of threatened preterm labor.
Methods: In this prospective, open-label, randomized controlled trial, women admitted to the hospital in threatened preterm labor (between 24 and 34 weeks' gestation) were randomized to receive atosiban or usual care (β-agonists, calcium channel blockers, magnesium sulphate, or any other tocolytic, alone or in combination, and/or bed rest).
Results: In women randomized to receive atosiban (n = 295) or usual care (n = 290), significantly more women receiving atosiban remained undelivered at 48 h with no alternative tocolytic compared with usual care (77.6% vs. 56.6%; $P < 0.001$). The proportion of women remaining undelivered after 48 h was comparable between the treatment groups. However, more women in the atosiban group required no additional tocolytics (85.1% vs. 62.8%; $P < 0.001$). Maternal and fetal safety was significantly superior with atosiban. Neonatal safety was comparable.
Conclusions: These findings support the use of atosiban to delay preterm birth and are consistent with previously conducted, randomized, controlled trials. Atosiban was associated with fewer maternal and fetal adverse events compared with other tocolytics, and presented no safety concerns for either the mother or the unborn baby.

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Introduction

The definition and impact of preterm birth

Preterm birth, defined as birth at <37 completed weeks' gestation [29], occurs in 5–10% of all pregnancies, leading to an estimated 13 million preterm deliveries worldwide [8]. Preterm birth contributes significantly to the incidence of perinatal death and long-term handicap, which can require lifelong care at considerable expense. Infants delivered prematurely are susceptible to life-threatening complications such as respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis, infection, jaundice, hypothermia and hypoglycemia [24].

Treatment of preterm labor

The goals of managing preterm labor are to minimize perinatal morbidity and mortality while preserving maternal health [15]. To date, tocolysis has not been convincingly demonstrated to improve neonatal outcome or survival. However, measures facilitated by the timely use of tocolytics, such as administration of a full course of corticosteroids to aid fetal lung maturation and *in-utero* transfer to a specialist unit where the newborn baby can receive optimal care, are associated with improved outcome [4, 13]. Thus, the current aim of tocolysis is to delay delivery long enough to allow these measures to be implemented; usually 48 h.

Several drugs have been used to treat preterm labor, including β-agonists. These drugs can prolong pregnancy for up to 48 h [7] but their non-specific mode of action results in an unfavorable side-effects profile, particularly with respect to maternal cardiovascular events. A recent guideline published by the Royal College of Obstetricians and Gynecologists (RCOG) has suggested the oxytocin receptor antagonist atosiban as an alternative, based on comparable efficacy and a superior maternal and fetal side-effects profile [23].

Although nifedipine is mentioned in the same RCOG guideline as an alternative for β-agonists, it is not licensed as a tocolytic and although the subject of randomized trials, most of the available data collated in meta-analyses and systematic reviews comprise smaller and often poor quality trials, which negatively impacts on

the validity of their conclusions [12, 14, 19]. There are no placebo-controlled trials of nifedipine and large follow-up studies on safety are lacking. Recently, there have been a number of anecdotal reports of serious pulmonary and cardiovascular events following the use of nifedipine or other calcium channel blockers as tocolytics [2, 9, 20, 26–28].

Atosiban has been compared with placebo and β-agonists in randomized controlled trials. Compared with placebo, significantly more women receiving atosiban remained undelivered after 48 h without the need for an additional tocolytic. There were no differences in the level of cardiovascular adverse events between the two groups [22]. Atosiban has been compared with the β-agonists ritodrine [17], salbutamol [3] and terbutaline [16] in three separate double-blind studies. All three studies were of a similar design, allowing the pre-planned analysis of the pooled data for β-agonists [18]. These trials demonstrated the comparable efficacy and superior safety profiles of atosiban compared with β-agonists [3, 16–18]. In two recent studies, including 80 [11] and 63 women [1], respectively, randomized to receive either atosiban or nifedipine, delivery at 48 h or seven days was not significantly different between the two treatments, although a trend in favor of atosiban was observed. However, atosiban was associated with significantly fewer maternal adverse events, particularly cardiovascular.

The indications for administration of atosiban in threatened preterm labor have been extrapolated from these clinical trials. However, it is important to continue to evaluate treatment success in real-life clinical practice. This trial [10] was designed to evaluate the efficacy and safety of atosiban compared with the usual care given to women admitted with threatened preterm labor in routine clinical practice.

Methods

Design

This was a randomized, open-label, prospective trial in pregnant women with threatened preterm labor, performed in 105 centers in six countries (Austria; France; Germany; Italy; Spain; UK).

Inclusion and exclusion criteria are given in Table 1. Women who satisfied these criteria were randomized to receive atosiban (Tractocile®; Ferring Pharmaceuticals, Lausanne, Switzerland) or usual care.

Randomization and treatment

Randomization was performed centrally by a call center. Usual care included treatment with β-agonists, calcium channel blockers, magnesium sulphate, or any other tocolytic, alone or in combination, and/or bed rest. Atosiban was not to be used as usual care. Women were randomized and treated on the day of hospital admission. A follow-up visit took place 48 h later followed by an end of study assessment at discharge. Data collected included details of concomitant medication, delivery details and maternal, fetal and neonatal safety information.

The standard protocol for atosiban administration was as follows; an initial bolus of 6.75 mg, followed by 300 μg/min for three hours, then 100 μg/min for up to 45 h. Three further re-treatments were permitted. The total dose given during a full course of atosiban therapy was not to exceed 330 mg. No restrictions were made on the use of concomitant medication, including tocolytics, prior to or during the study.

Efficacy and safety assessment

The primary efficacy endpoint was defined as the proportion of women remaining undelivered and not requiring an alternative tocolytic within 48 h of randomization. Alternative tocolytic was defined as the second pharmacological agent given. Re-treatment with atosiban was not considered as an alternative tocolytic nor was the first tocolytic given in women managed conservatively by bed rest.

The secondary efficacy endpoints were: proportion of women remaining undelivered 48 h after randomization; proportion of women who did not receive an alternative tocolytic within 48 h; proportion of women re-treated with atosiban; number of re-treatments with atosiban; number of atosiban re-treatments in women undelivered and not requiring an alternative tocolytic within 48 h; proportion of women receiving a full course of steroids; time to delivery or first use of an alternative tocolytic; time to delivery; delivery characteristics; satisfaction of women at discharge (pleasant, indifferent, unpleasant).

Safety was evaluated by recording the occurrence of adverse and serious adverse events in the mother, fetus and neonate. Each adverse event was graded (mild, moderate, and severe)

Table 1 Summary of inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Women ≥18 years of age • Gestational age between 24 and 33[1] completed weeks • Regular uterine contractions lasting a minimum of 30 s at a rate of ≥4 per 30 min • Cervical dilatation of 1–3 cm for multiparous women or 0–3 cm for nulliparous women and effacement of ≥50% • Signed informed consent	• Antepartum uterine hemorrhage • Eclampsia or severe pre-eclampsia requiring delivery • Intrauterine fetal death • Placenta previa • Any other condition of the mother or fetus in which continuation of the pregnancy was hazardous • Known hypersensitivity to the active substance or any of the agents • Premature rupture of the membranes >30 weeks' gestation • Intrauterine growth retardation and/or abnormal fetal heart rate

[1]Defined as 24 weeks+0 days to 32 weeks+6 days.

and its relationship to the administered medication assessed (unrelated, unlikely, possible, probable). Serious adverse events were defined as any untoward medical occurrence that resulted in death; was life threatening; required continued hospitalization; resulted in persistent or significant disability or incapacity; was a congenital anomaly or birth defect; was an important medical event. Serious adverse events included pulmonary edema, hemorrhage and deep vein thrombosis (maternal), bradycardia, heart rate decelerations and tachycardia (fetal) and meconium ileus, bradycardia and anemia (neonatal). Women were analyzed according to the treatment received. Adverse events were regarded as "pre-treatment" if they occurred between randomization and the start of study treatment and "treatment-emergent" if they occurred in the time interval between the start of study treatment and the final visit.

The trial protocol was approved by the Ethics Committees of the participating centers and conducted in accordance with the principles outlined in the Declaration of Helsinki [30] and Good Clinical Practice. Signed informed consent was obtained from each participant at enrolment.

Power calculation and statistical analyses

The pooled results from previous clinical studies of atosiban versus β-agonists demonstrated a 4% difference in terms of efficacy using the primary efficacy endpoint of non-delivery without the need for alternative tocolysis within 48 h. Due to the open-label nature of the present trial, the previously reported superior safety profile of atosiban was expected to be more obvious, therefore, decreasing the number of patients stopping atosiban for safety reasons. In addition, the provision for bed rest (i.e., no active pharmacological agent) as part of usual care, suggested that the efficacy in this group could be slightly lower than that reported in clinical studies using active reference tocolytics. Thus, the trial was designed to detect a possible difference of 9%. To test this difference with a significance level of 5% and power of 80%, 800 women were required in the study.

The Cochran Mantel Haenszel test, adjusted by country, was used to analyze the primary and secondary efficacy endpoints. Odds ratios and 95% confidence intervals (CI) were used to assess treatment effect. Logistic regression analysis of the primary endpoint was performed and adjusted for randomization stratification factors (i.e., gestational age, order (singleton or multiple), gravidity and premature rupture of the membranes [PROM]).

Results

Ninety-one centers from six European countries recruited a total of 585 women (Austria, n = 48 [8.2%]; France, n = 151 [25.8%]; Germany, n = 212 [36.2%]; Italy, n = 37 [6.3%]; Spain, n = 119 [20.3%]; UK, n = 18 [3.1%]), who were randomized to receive atosiban (n = 295) or usual care (n = 290; Figure 1).

Five women (1.7%) in the atosiban arm and four (1.4%) in the usual care arm withdrew their consent and one woman in the usual care arm only had the admission visit. Baseline demographics and general physical examination characteristics were not significantly different between the two treatment arms (Table 2). Interestingly, whereas most women underwent vaginal ultrasound (62.9%), very few were tested for fetal fibronectin (8.9%). Obstetric histories were similar between the two treatment arms.

The difference in efficacy was larger than the predicted 9% and the study was closed, due to recruitment difficulties, when 585 women had been entered. Primary analyses were performed on the intention-to-treat (ITT) population.

Efficacy assessments

Primary efficacy endpoint The proportion of women remaining undelivered and not requiring an alternative tocolytic within 48 h of randomization was significantly higher with atosiban (77.6%; n = 229/295) compared with usual care (56.6%; n = 164/290) ($P < 0.001$). These significant differences remained unchanged in the subgroups of women with single pregnancies, at both low and high gestational ages and for women without PROM (Table 3).

The initial treatments in the usual care arm were a β-agonist (64.5%; n = 187/290), a calcium channel blocker (14.8%; n = 43/290) or a β-agonist with magnesium (10.0%; n = 29/290). The proportions of these women remaining undelivered and not requiring an alternative tocolytic within 48 h were 55.6% (n = 104/187), 65.1% (n = 28/43) and 51.7% (n = 15/29), respectively.

Secondary efficacy endpoints No significant differences were observed between atosiban and usual care with respect to women remaining undelivered after 48 h of randomization overall (90.2% vs. 91.0%; P = NS) or in the subgroups of women given β-agonists (90.9%; n = 170/187), β-agonists with magnesium (96.6%; n = 28/29) or calcium channel blockers (90.7%; n = 39/43).

There was, however, a significantly higher proportion of women in the atosiban arm (85.1%; n = 251/295) compared with the usual care arm (62.8%; n = 182/290) who

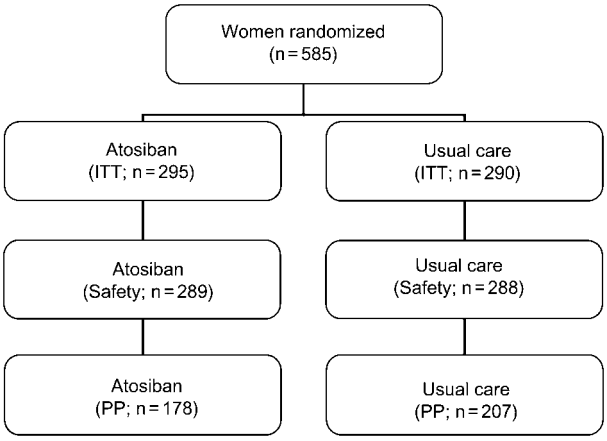

Figure 1 Trial profile; distribution of women.
Women satisfying the criteria in Table 1 were randomized to receive atosiban (n = 295) or usual care (n = 290).

Table 2 Summary of baseline demographics and physical examination characteristics (n = 585).

	Atosiban (n = 295)	Usual care (n = 290)
Baseline demographics		
Age of mother (years)		
Mean	29.02	29.3
Median	29	30
Range	16–42	19–45
Gestational age (weeks)		
Mean	29.52	29.53
SD	2.67	2.6
Median	30	30
Range	23–33	23–33
In classes		
≤28 weeks + 6 days	97 (32.9%)	95 (32.8%)
≥29 weeks + 0 day	198 (67.1%)	195 (67.2%)
Pregnancy order		
Singleton	231 (78.3%)	228 (78.6%)
Multiple pregnancy[1]	64 (21.7%)	62 (21.4%)
Twins	63	56
Triplets	1	5
Previous preterm deliveries		
Yes	28 (9.5%)	26 (9.0%)
No	267 (90.5%)	264 (91.0%)
PROM[2]		
Present	11 (3.7%)	11 (3.8%)
Absent	284 (96.3%)	278 (96.2%)
Baseline physical examination characteristics		
Cervical dilatation (cm)		
Mean	0.94	1.06
Median	1	1
Range	0 – 6	0 – 4
Cervical effacement		
0%	6 (2.0%)	9 (3.1%)
50%	185 (62.7%)	170 (59.0%)
75%	90 (30.5%)	91 (31.6%)
100%	14 (4.7%)	18 (6.3%)
Contraction frequency (per 30 min)		
Mean	7.67	7.50
Median	6	6
Range	1 – 30	0 – 18

[1]Information on number of fetuses not available for one woman with a multiple pregnancy.
[2]Data unavailable for one woman in the usual care arm.

did not receive an alternative tocolytic within 48 h of randomization ($P < 0.001$). This was the case for single pregnancies (87.0% vs. 63.6%; $P < 0.001$), high (87.6% vs. 54.7%; $P < 0.001$) and low (83.8% vs. 66.7%; $P < 0.001$) gestational age and women without PROM (85.2% vs. 62.6%; $P < 0.001$). There were too few women in the PROM group for meaningful comparison. Within the usual care arm, no alternative tocolytic was given within 48 h of randomization in 61.5% (n = 115/187) of women receiving β-agonists, 51.7% (n = 15/29) receiving β-agonists with magnesium and 74.4% (n = 32/43) receiving calcium channel blockers.

The mean total dose of atosiban administered to women was 368.25 mg. In the atosiban arm, the mean durations of administration, alternative tocolytic administration and total treatment were 2.88, 12.56 and 5.58 days, respectively. Most women in the atosiban arm either received no further treatment or were re-treated with atosiban (64%; n = 185/289). Of those women re-treated, the majority received one or two re-treatments. In women who received atosiban initially, the most frequently used second-line tocolytics were β-agonists (15.6%; n = 45/289), magnesium (9.7%; n = 28/289) or calcium channel blockers (6.9%; n = 20/289). In the usual care arm, of the 187 women who received a β-agonist initially, 63.6% (n = 119/187) received no alternative tocolytic, 20.3% (n = 38/187) went on to receive second-line treatment with magnesium and 7.0% (n = 13/187) with a calcium channel blocker. Of the 43 women who received a calcium channel blocker initially, 51.2% (n = 22/43)

Table 3 Proportion of women who remained undelivered and who did not receive an alternative tocolytic within 48 h of randomization (ITT population).

	Atosiban	Usual care	Odds ratio (95% CI)	P-value[1]
Primary efficacy endpoint	229/295 (77.6%)	164/290 (56.6%)	2.78 (1.92, 4.02)	<0.001
Pregnancy order				
Singleton	186/231 (80.5%)	130/228 (57.0%)	3.36 (2.18, 5.18)	<0.001
Multiple	43/64 (67.2%)	34/62 (54.8%)	1.47 (0.70, 3.10)	0.30
Gestational age				
≤28 weeks+6 days	77/97 (79.4%)	44/95 (46.3%)	4.42 (2.31, 8.45)	<0.001
≥29 weeks+0 days	152/198 (76.8%)	120/195 (61.5%)	2.17 (1.38, 3.43)	<0.001
PROM				
Yes	5/11 (45.5%)	4/11 (36.4%)	Numbers too small to calculate	
No	224/284 (78.9%)	160/278 (57.6%)	2.92 (1.99, 4.29)	<0.001

[1]Mantel Haenszel χ^2 test (including country adjustment).

received no alternative tocolytic, 23.3% (n=10/43) went on to receive a spasmolytic drug and 18.6% (n=8/43) went on to receive atosiban. Of the women who received a β-agonist with magnesium, 79.3% (n=23/29) received no alternative tocolytic and 20.7% (n=6/29) received second-line treatment with atosiban.

Although significantly more women received steroids post-randomization in the atosiban arm (177/295 [60%] vs. 146/290 [50.3%] P=0.02), there were no significant differences in the number of women receiving a full course. Delivery characteristics (Table 4), time to delivery and first use of an alternative tocolytic were all comparable between the two treatment arms.

In terms of overall satisfaction, significantly more women randomized to atosiban reported treatment as "pleasant" compared with usual care at 48 h from randomization (59.6% vs. 27%; P<0.001) and at discharge (57.1% vs. 31.0%; P<0.001). Whereas the majority of women in the atosiban arm rated their treatment as "pleasant" at 48 h (59.6%; n=171/287) and discharge (57.1%; n=165/289), the majority of women in the usual care arm were indifferent to their treatment at these times (49.6%; n=138/278 and 53.8%; n=149/277, respectively).

Safety assessments

Safety analysis was performed on all women who were randomized, who had received active treatment and for whom the presence or confirmed absence of adverse events was available (n=577). A summary of treatment-emergent adverse events and serious adverse events by actual initial treatment is presented in Table 5.

Maternal safety Significantly fewer women had maternal treatment-emergent adverse events after initial treatment with atosiban compared with other treatments (P=0.01; Table 5). The most frequently reported treatment-emergent adverse events were cardiac (5.9% for atosiban and 35.3% for other treatments) and gastrointestinal disorders (21% for atosiban and 20% for other treatments). The incidence of serious adverse events was higher in the other treatment group compared with atosiban, but the difference was not significant (P=0.17).

The design of the study allowed women to be given more than one pharmacologic agent for tocolysis. Therefore, a true evaluation of treatment-emergent adverse events with atosiban is impossible. Comparisons were, therefore, made according to the actual treatment received (Table 6). Overall, a lower proportion of women had maternal treatment-emergent adverse events after receiving atosiban alone (223 events reported in 105/195 [53.8%] women) compared with any other tocolytic alone (270 events reported in 110/172 [64.0%] women). In particular, maternal tachycardia was reported in substantially more women receiving any other tocolytic alone, compared with atosiban (28.5% vs. 1.5%). No maternal deaths were reported.

Fetal safety Significantly more fetal treatment-emergent adverse events were reported in the other treatment group than in the atosiban group (13.6% vs. 8.5%; P=0.03). This difference was due largely to a lower incidence of fetal tachycardia in the atosiban group (2.3% vs. 6.6%). Evaluation of treatment received also indicated a lower rate of fetal tachycardia with atosiban alone (2.1%) compared with any other initial tocolytic alone (7.0%; Table 6). There were more treatment-emergent serious adverse events in fetuses in the other treatment group, but the difference was not significant (P=0.18).

There were three intrauterine deaths, one in the atosiban arm and two in the other treatment arm. The intrauterine death in the atosiban arm occurred in a fetus with Potter's syndrome prior to inclusion in the trial. One of the fetal deaths in the other treatment arm occurred at an extremely low gestational age (23 weeks+4 days) and the reason for the other was not apparent.

Neonatal safety No difference in the overall incidence of adverse events or in the incidence of individual

Table 4 Delivery characteristics (ITT population).[1]

	Atosiban (n = 295)	Usual care (n = 290)
Delivery		
N	295	290
During study	83 (28.1%)	98 (33.8%)
After study	199 (67.5%)	179 (61.7%)
Not recorded	13 (4.4%)	13 (4.5%)
Duration of labor (h)		
N	89	96
Mean	4.25	6.01
SD	4.00	11.13
Median	3.00	3.13
Range	0–19	0–98
Gestational age at delivery (weeks)		
N	282	277
Mean	35.72	35.44
SD	4.02	4.05
Median	36.86	36.14
Range	24.0–41.7	23.6–41.6
Mode of delivery		
N	282	277
Normal vaginal	182 (64.5%)	173 (62.5%)
Instrumental	9 (3.2%)	11 (4.0%)
Cesarean	91 (32.3%)	93 (33.6%)

[1]Since data collection was not controlled, women who delivered after the end of the study may not have had their delivery details recorded.

adverse events was observed between atosiban and other treatments. The two most common serious adverse events cited were prematurity and respiratory distress syndrome, which were comparable between the two treatment arms and together accounted for 60.4% n = 247/409 events reported.

Twelve neonatal deaths occurred; three babies born to women receiving atosiban and nine born to women receiving other medications. The majority of the neonatal deaths occurred at lower gestational ages ($\leq$29 weeks; n = 10). The two neonatal deaths at 29 weeks or later were in infants not exposed to atosiban. None of the deaths was considered by the investigators to be related to the study medication.

Discussion

The principal objective of the trial was to evaluate the efficacy of atosiban compared with usual care in the management of threatened preterm labor in a "real-life" clinical setting. The study was, therefore, kept as flexible as possible in order to minimize interference with routine clinical practice. Consequently, evaluation was kept as simple as possible, focusing on global outcomes and safety assessments and avoiding the extra burden of protocol-induced evaluation and laboratory or explanatory medical procedures. This, however, is associated with some limitations. In particular, the protocol did not define any criteria for the use of rescue treatment and

Table 5 Summary of treatment-emergent adverse events and serious adverse events by actual initial treatment (N [%] E).[1]

	Atosiban[2] (n = 305)	Other (n = 272)	OR (95% CI)	P-value[3]
Maternal				
Adverse events	187 (61.3%) 445	189 (69.5%) 524	0.63 (0.44, 0.90)	0.01
Serious adverse events	31 (10.2%) 36	37 (13.6%) 47	0.69 (0.41, 1.17)	0.17
Fetal				
Adverse events	26 (8.5%) 31	37 (13.6%) 54	0.56 (0.33, 0.95)	0.03
Serious adverse events	12 (3.9%) 15	17 (6.3%) 18	0.60 (0.28, 1.28)	0.18
Neonatal				
Adverse events	81 (26.6%) 473	73 (26.8%) 429	0.94 (0.65, 1.37)	0.75
Serious adverse events	77 (25.2%) 209	68 (25.0%) 200	0.96 (0.65, 1.40)	0.82

[1]N = number of women; E = number of events.
[2]Includes women receiving atosiban as part of "usual care".
[3]Mantel Haenszel χ^2 test (including country adjustment).

Table 6 Maternal, fetal and neonatal treatment-emergent adverse events by actual treatment received (n = 577[1]).

Adverse events	Atosiban alone (n = 195)	First tocolytic alone (not atosiban) (n = 172)
Maternal		
Adverse events	105 (53.8%) 223	110 (64.0%) 270
Tachycardia	3 (1.5%) 4	49 (28.5) 54
Constipation	8 (4.1%) 8	9 (5.2%) 9
Nausea	11 (5.6%) 11	5 (2.9%) 5
Headache	16 (8.2%) 17	12 (7.0%) 12
Tremor	–	11 (6.4%) 11
Anxiety	5 (2.6%) 6	8 (4.7%) 8
Dyspnoea	1 (0.5%) 1	8 (4.7%) 8
Fetal		
Adverse events	14 (7.2%) 18	20 (11.6%) 35
Bradycardia	5 (2.6%) 5	5 (2.9%) 8
FHR deceleration	–	3 (1.7%) 3
Tachycardia	4 (2.1%) 5	12 (7.0%) 17
Neonatal		
Adverse events	40 (20.5%) 206	42 (24.4%) 227
Anemia	7 (3.6%) 7	6 (3.5%) 8
Bradycardia	3 (1.5%) 4	10 (5.8%) 12
Hyperbilirubinemia	5 (2.6%) 5	7 (4.1%) 13
Jaundice	13 (6.7%) 16	9 (5.2%) 14
RDS	27 (13.8%) 34	30 (17.4%) 38

[1]Nine women received no active treatment.

thus decisions made in this regard were based entirely on the investigator's choice, which may have introduced bias.

The composite or dual primary efficacy endpoint of women remaining undelivered and not requiring an alternative tocolytic 48 h after randomization reflects both the efficacy and tolerability of the treatment [18]. Compared with usual care, a significantly greater proportion of women randomized to atosiban remained undelivered without the need for an alternative tocolytic. This can be explained by a superior tolerability of atosiban compared with usual care, since there was a significant difference in the proportion of women requiring an alternative tocolytic within 48 h of randomization but the proportion of women remaining undelivered was comparable. The tolerability of atosiban was supported by superior patient satisfaction compared with usual care.

One of the goals of tocolytic therapy is to delay delivery in order to enable administration of a full course of steroids [6]. In this trial, the proportion of women receiving a full course of steroids was similarly low between treatment groups. This could be explained by the administration of steroids not being mandatory and being left to the judgment of the physician. In current practice, steroid administration is much more common than reflected by this trial [5]. The observation that significantly more women randomized to atosiban compared with usual care received any steroids may have contributed to the numerically lower incidence of respiratory distress syndrome in babies born to these women.

A recently published systematic review associated atosiban with an increase in infant deaths up to 12 months of age [21]. The single trial on which this association was based [22] had imbalanced study populations whereby gestational age was significantly lower in the women randomized to receive atosiban than those given placebo. The findings of this review are in contrast to the present study, in which none of the perinatal deaths was attributed to tocolytic therapy as well as data from previously conducted randomized controlled trials [18]. Furthermore, there was no excess mortality in the offspring of women who received atosiban.

The increased incidence of maternal adverse events with other treatments, such as tachycardia, palpitations, tremor and dyspnea is mainly due to the β-agonists used. Indeed, the comparison of adverse events by actual treatment received supports this. The adverse events in women receiving atosiban are similar to those previously reported from randomized controlled trials [18]; maternal tachycardia (5.5%); nausea (11.9%); headache (9.7%); anxiety (1.1%); tremor (1.4%); respiratory distress syndrome (19.5%); fetal bradycardia (5.7%) and fetal anemia (7.6%). In that study, women were switched to alternative tocolytics mainly due to treatment failure or lack of tolerability. Not surprisingly there was a higher incidence of adverse events in the treatment groups when more than one tocolytic agent was administered.

In previous studies, non-significant differences in terms of superior fetal safety were observed with atosiban compared with β-agonists [18], largely as a result of a higher

incidence of β-agonist-induced fetal tachycardia. Fetal side effects, in particular fetal tachycardia, have been reported to cause discontinuation of tocolysis with β-agonists [25]. Discontinuation of an efficacious tocolytic drug due to fetal adverse events could impact on the delivery rate and influence neonatal outcome. The significantly superior fetal tolerability of atosiban versus other tocolytics reported in this clinical trial is, therefore, of importance.

Conclusions

Atosiban resulted in more women remaining undelivered and not requiring an alternative tocolytic agent after 48 h and was associated with fewer maternal and fetal adverse events.

The findings of this clinical trial support the use of atosiban for delaying imminent preterm birth. They confirm the results of randomized controlled trials comparing the efficacy and safety of atosiban with β-agonists and are in line with earlier placebo-controlled trials.

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