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ACTA REVIEW

Development and clinical experience with the new evidence-based tocolytic atosiban

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The incidence of preterm birth has remained unchanged for the last few decades. This is due, in part, to the complex etiology of preterm labor, and the limited ability of tocolytic agents to prolong pregnancy as a result of limited efficacy and poor safety profiles. The recent introduction of the oxytocin antagonist, atosiban, represents a new generation of uterine-specific tocolytics, which are associated with more favorable safety profiles. This paper discusses the rationale behind the development of the oxytocin antagonists and provides a review of the phase II and III trials that have investigated atosiban. Also included is a retrospective analysis of 83 women assessed in the Vienna Medical School, providing an insight into the benefits associated with atosiban in the everyday clinical setting.
The introduction of a safer tocolytic agent offers the potential to change the current approach to the management of preterm labor. This includes a prolonged period of treatment at earlier or later gestational ages and possibly an extended use to women with contraindications who would normally have been excluded from treatment, e.g. preterm premature rupture of the membranes.

Keywords: atosiban, evidence-based tocolytic, preterm labor

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The incidence of preterm birth has remained unchanged over the last few decades (1). One of the reasons for this is the heterogeneous nature of preterm labor, which explains why there is no singular tocolytic treatment capable of delaying pregnancy until term. Tocolytic drugs are also limited by the fact that a large proportion of women are ineligible for treatment because of gestational age, contraindications or iatrogenic reasons.

The practice of suppressing preterm labor by pharmacologic intervention has been used for over 40 years. The first class of drugs to be introduced as tocolytic agents were the nonselective β-agonists in the 1960s. However, the earliest β-agonist, isoxsuprine, was restricted in its clinical use because of widespread side-effects (2). A few years later intravenous alcohol was proposed as a potential tocolytic agent based on its ability to suppress the release of oxytocin from the hypothalamus (3). Not surprisingly, alcohol also never gained clinical acceptance on account of its questionable efficacy and significant maternal side-effects.

Despite these initial setbacks, a number of different pharmacologic alternatives have been used in the clinical setting since the 1980s, although most were used off-license. The tocolytic agents available include the more selective β_2-agonists, calcium channel blockers, magnesium sulfate, and prostaglandin synthetase inhibitors. None of these agents were initially designed as tocolytic drugs, although their widespread mechanism of action included the ability to suppress uterine contractions, so consequently they were recruited into the tocolytic armamentarium. None of these conventional agents are supported by strong evidence-based medicine because they were never licensed to treat women in preterm labor, with the exception of the β-agonists which were originally developed as a treatment for asthma. Despite the longevity of the β-agonists, there have been few studies designed to

evaluate their efficacy and safety in the treatment of preterm labor. Evidence from early studies appeared to suggest that the β-agonists were capable of significantly delaying delivery beyond 7 days (4–6). However, subsequent studies were only capable of demonstrating a delay of 48 h, which implied that poor trial design was responsible for the earlier long-term success (7, 8). Therefore, clinical acceptance of these drugs has mainly been based on anecdotal or empiric evidence. More importantly, they are still associated with a number of side-effects, some of which are life threatening, particularly pulmonary edema.

The recent introduction of the oxytocin antagonist, atosiban, heralds the arrival of the first evidence-based drug for the treatment of preterm labor, which specifically targets the uterus. As a result of its specificity, atosiban is associated with fewer side-effects compared with the existing conventional tocolytics.

The aim of this review is to discuss the rationale behind the development of atosiban, to summarize the phase II and III study data, and to report on recent everyday clinical experiences with atosiban from the Vienna Medical School.

Development of the oxytocin antagonists

Physiologic role of oxytocin

Oxytocin is a nonapeptide, which is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is stored in neurosecretory granules in the posterior pituitary gland, where it is released by various stimuli, including mechanic stimulation of the nipples, cervical and vaginal dilatation and the presence of other hormones, such as estrogen, prostaglandins and thyrotrophin-releasing hormones (9).

Oxytocin has long been established as a valuable therapy for labor induction. However, its precise physiologic role during labor and preterm labor has only recently been elucidated. The main physiologic role of oxytocin is the induction of labor, although evidence suggests additional involvement in the initiation and maintenance of labor. Although the mean oxytocin concentration does not rise significantly during the onset of labor there is sufficient evidence to suggest that the uterus becomes increasingly sensitive to oxytocin as a result of a rise in oxytocin receptor numbers (10, see Fig. 1). Receptor numbers have been shown to reach a maximum after the onset of spontaneous contractions, either at term or preterm (11). Uterine response has been shown to be directly correlated with the proportion of oxytocin receptors in the uterus, which suggests that oxytocin plays an active role in the process of initiating labor despite levels remaining fairly static before parturition. Although oxytocin is regarded as the primary initiator of labor, it is also important to note the contribution made by vasopressin via the vasopressin receptors in the myometrium, which may mediate an additional regulatory role in preterm and term labor (12, 13). The presence of these two hormones in the myometrium may explain the heterogeneity observed in terms of oxytocin receptor expression in the term myometrium (14) and may explain the varied etiology of preterm and term uterine contractions.

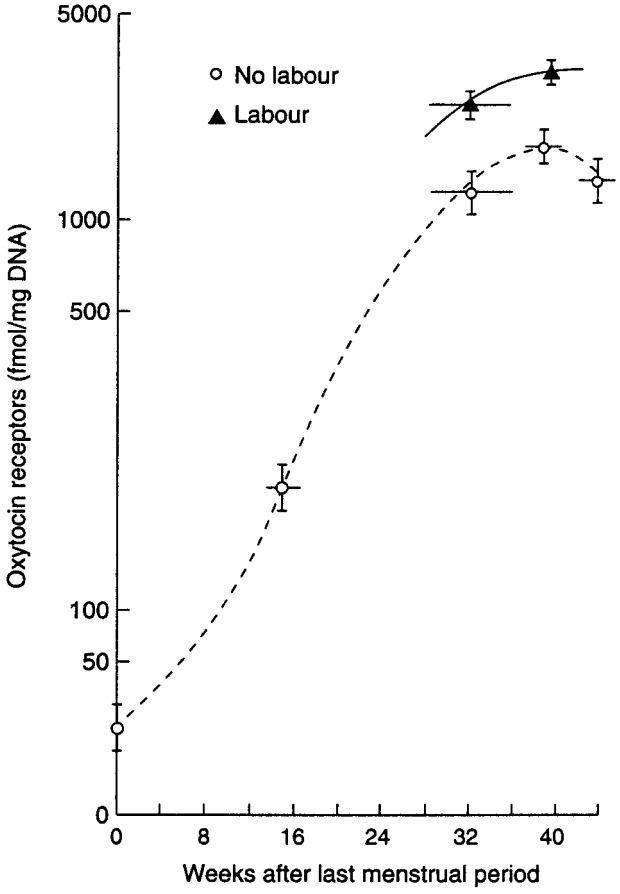

Fig. 1. Oxytocin receptor concentration in human myometrium during pregnancy and during term and preterm labor. Figure reproduced from [10] with kind permission from Elsevier Science.

The fundamental difference between preterm and term labor is thought to be that the latter is initiated by physiologic activation of key components in the common terminal pathway, while preterm labor is triggered by a pathologic disease process, which again activates components of the terminal pathway (15). Preterm labor can be regarded as a syndrome with disparate causes and effectors. In normal pregnancy, it is reasonable to assume

that prostaglandins produced via decidual activation, and in response to a cytokine cascade, act on the myometrium, which is prepared for labor by uterotrophins. Locally produced oxytocin may play a role in the process of labor while systemic oxytocin may contribute to the expulsion of the placenta and postpartum changes in myometrial contractility. Possible triggers suggested for preterm labor are infection, stress-induced release of corticotrophin releasing hormone and prostaglandin-dehydrogenase deficiency (16).

There are a number of factors to support the assumption that oxytocin is essential for the initiation of labor:

1) oxytocin is the most potent and specific stimulus to the pregnant human uterus;
2) in animal studies, the secretion of oxytocin is clearly associated with the initiation of labor;
3) at term, exogenous oxytocin is extremely effective at inducing labor in women;
4) deficiencies of the posterior lobe are associated with abnormal length pregnancies; and
5) ethanol, which inhibits oxytocin release, has been used successfully to treat preterm labor.

Oxytocin receptors are known to increase during labor in the myometrium and also the decidua. As the decidua possesses a high level of prostaglandin synthetase activity, it is likely that oxytocin influences the production of prostaglandin in this tissue. *In-vitro* studies support this theory showing significant increases in the production of prostaglandin E and F in the decidua (17), while studies in pregnant women confirm that oxytocin induces a rise in the levels of plasma prostaglandin E and F, which potentiate uterine contractions and cervical dilatation (18, 19).

A significant proportion of oxytocin is believed to exert its effect via a paracrine mechanism whereby oxytocin originates in the amnion, decidua and chorion (20, 21), a theory, which is supported by the fact that only very low levels of maternal plasma oxytocin can be detected throughout gestation.

It is widely acknowledged that oxytocin is also generated by the fetus. Marked arteriovenous differences in the umbilical vessels after spontaneous labor suggest that the fetus secretes considerable amounts of oxytocin during labor. Thus it appears that the fetus plays an active role in triggering its own delivery.

Rationale for an oxytocin antagonist

Oxytocin became the first peptide hormone to be used in a clinical setting and has several potential clinical roles. Target organs for oxytocin include the mammary gland and the uterus, and oxytocin analogs could potentially be used to treat conditions such as agalactia, postpartum hemorrhage and preterm labor. It is now known that oxytocin can stimulate contractions of the uterus in term and preterm labor through several mechanisms of action. These include an increased oxytocin receptor concentration, pulsed release of oxytocin from the posterior pituitary, or secretion from peripheral tissues and enhanced prostaglandin release from decidua and fetal membranes.

The development of oxytocin agonists and antagonists began soon after the oxytocin molecule had been characterized through the work of du Vigneaud et al. in 1953 (22). In 1960 it was discovered that a minor modification at position 2 of the oxytocin molecule could lead to partial uterotonic antagonism (23). Further changes produced a series of analogs, which were capable of full antagonism in animal experiments. *In-vitro* testing on human myometrial tissue revealed that the deaminated analogs were the most effective (24). Final modifications at positions 1, 2, 4 and 8 produced a series of analogs with a higher affinity for human myometrium (25). The most effective antagonist, based on its ability to inhibit vasopressin-stimulated uterine contractions, was atosiban [1-deamino-2-D-Tyr-(O-Et)-4-Thr-8-Orn] (26, 27). Furthermore, vasopressin-induced decreases in uterine blood flow and increases in uterine activity were reversed following atosiban administration, thus supporting a therapeutic role for primary dysmenorrhoea and preterm labor (28). Atosiban acts as an oxytocin antagonist by competing with oxytocin for receptor sites in the myometrium and possibly decidua and fetal membranes. The result is a dose-dependent suppression of uterine contractility. Although atosiban shares an affinity for vasopressin receptors because of the close chemical homology between vasopressin and oxytocin, this does not present a significant problem (Fig. 2). This is prob-

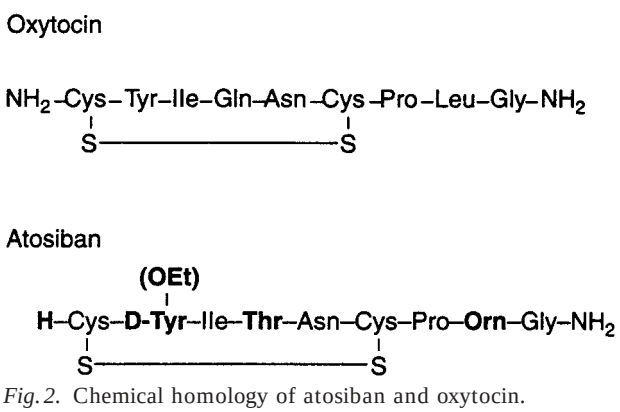

Fig. 2. Chemical homology of atosiban and oxytocin.

ably explained by the substantial increase in the number of oxytocin receptors in the uterus during labor, while there is no concomitant rise in vasopressin receptor numbers.

The key principle in the development of atosiban for treating preterm labor is its uterine specificity. All of the current tocolytics have systemic effects with multiorgan side-effects. Preliminary *in-vivo* studies in humans were encouraging. In 13 women with uncomplicated preterm labor, 10–100 μg/min of atosiban for 1–10 h inhibited uterine activity in all patients (29). A subsequent study in 12 women with uncomplicated preterm labor investigated the effect of atosiban, administered for 1.5–13 h, on uterine contractions. In nine patients, inhibition of uterine contractions was achieved and progression in cervical scores arrested (30). No side-effects were observed in either of the studies. These early studies demonstrated the therapeutic potential for atosiban in the treatment of preterm labor.

Evidence-based tocolysis

Atosiban represents the first rationally designed tocolytic that has undergone the most thorough assessment in clinical trials. It is supported by the strongest evidence-based medicine compared with any of the other tocolytics.

Phase II trials

Initial phase II studies were designed to establish the most appropriate dose of atosiban required to inhibit uterine contractions and to assess efficacy. A total of three studies investigated atosiban in the clinical setting. The first of this series of studies was aimed at evaluating the efficacy and safety of atosiban in decreasing or arresting uterine contractility in women with threatened preterm labor (31). A double-blind, placebo-controlled, randomized trial investigated, as the primary outcome, the percentage change in the number of uterine contractions during a 1-h period compared with a subsequent 2-h treatment period. Secondary efficacy end-points assessed the proportion of women whose contractions ceased during treatment, and changes in cervical dilation and effacement. Results were encouraging for atosiban, with 77% of women receiving the study drug experiencing a reduction of $\geq$ 40% in the number of uterine contractions compared with 32% of women receiving the placebo. Women at later gestational ages responded to treatment more effectively than the placebo, which became significant in women beyond 31 gestational weeks ($p < 0.05$). A similar trend was observed for the secondary end-points, with a greater proportion of women treated with atosiban experiencing complete cessation of uterine contractions compared with the placebo (25 vs. 5%, $p < 0.05$).

In the second phase II trial, data were collated from four similarly designed, non-controlled, substudies, which assessed the ability of atosiban to suppress uterine contractions. A total of 62 women were treated with i.v. atosiban for up to 12 h. The primary efficacy end-point was the cessation of uterine contractions and successful tocolysis, which was defined as not requiring alternative rescue therapy, the absence of another episode of preterm labor and a delay of delivery for 48 h. Uterine contractions were inhibited in 61% of the women while successful tocolysis was reported in 70% of the women receiving atosiban (32).

The final phase II study was designed to determine the minimal effective dosage regimen for atosiban in the treatment of acute preterm labor and to assess the effect of adding a bolus dose before infusion (33). A total of 302 women were allocated to five treatment groups (four were double-blind atosiban treated groups and the fifth was an open-label ritodrine group). The primary efficacy measure was the proportion of women experiencing a cessation of uterine contractions for 1 h or more during infusion. Other measures included ≤ 4 contractions per hour in the last hour of therapy, percentage decrease in the contraction rate from the start to the end of treatment, changes in cervical dilation and effacement, and discontinuation resulting from adverse events. The lowest dose of atosiban (0.6 mg plus 30 μg/min) was significantly less effective than ritodrine, however this dose had no clinical relevance. The remaining atosiban regimens were all shown to be comparable with ritodrine. The use of a bolus dose resulted in a significantly greater proportion of patients who stopped contracting within the first 2 h of treatment (17/63) compared with those not receiving a bolus dose (6/58) ($p = 0.017$). Regarding adverse events, atosiban was discontinued in only one patient out of 244 (0.4%) compared with 15 out of 58 (25.8%) patients receiving ritodrine. In summary, the phase II trials suggest that atosiban is an effective tocolytic agent for the prevention of uterine contractility compared with placebo and ritodrine. Furthermore, its effect on uterine activity is enhanced by a bolus injection. Safety results from the trials were also encouraging, with only minor side-effects reported and a more favorable safety profile than ritodrine.

Phase III trials

The phase III trial program consisted of two placebo-controlled studies and three comparative

studies with the β-agonists. In the first of the placebo-controlled studies, the primary end-point was the time from the start of treatment to delivery or therapeutic failure (34). Secondary measures included the proportion of women remaining undelivered and who did not require alternative tocolysis at 24, 48 h and 7 days. No significant differences were reported for the primary end-point between atosiban and placebo. However, it is worth noting that for a number of prognostic factors there was a skewed distribution between the treatment groups, which may have contributed towards the lack of difference observed, i.e. women at <26 gestational weeks with a Bishops score ≥ 4 (15% placebo vs. 54% atosiban), gestational age <26 weeks (5% placebo vs. 10% atosiban) and alternative tocolysis (42% atosiban vs. 51% placebo). Alternative tocolysis was allowed after only 1 h of treatment had elapsed and, furthermore, the criteria for administering rescue therapy were not met in a large proportion of women. Despite these differences, significantly more women in the atosiban group remained undelivered without requiring alternative tocolysis at 24 h, 48 h and 7 days. Maternal adverse events and infant outcomes with atosiban were comparable with the placebo. Although there were more infant deaths in the atosiban group, this was attributed to an imbalance in randomization whereby a significantly greater number of women below 26 gestational weeks, with more advanced preterm labor, were included in the atosiban group. However, despite the limitations in study design, atosiban demonstrated superior efficacy than placebo for the secondary end-points after 24 h, 48 h and 7 days.

The second placebo-controlled study compared the efficacy of atosiban as a maintenance therapy with placebo in women who had achieved uterine quiescence with initial atosiban therapy (35). A total of 513 women received maintenance therapy, administered as a continuous subcutaneous infusion up to 36 gestational weeks. The primary end-point was the number of days from the start of maintenance therapy until the first recurrence of labor. The secondary end-point was the percentage of patients receiving subsequent intravenous atosiban therapy. Atosiban was shown to prolong the interval of time to the first recurrence of labor compared with placebo (32.6 days vs. 27.6 days; $p = 0.02$) and reduced the need for subsequent i.v. therapy for recurrent preterm labor (23% atosiban vs. 31% placebo). Maternal adverse events and infant outcomes were comparable between the treatment groups.

The second stage of the phase III study program involved three multinational, multicenter, randomized, comparative trials each comparing atosiban with one of three β-agonists (terbutaline, salbutamol or ritodrine) (36–38). As each trial shared the same study protocol, the overall assessment of efficacy and safety was based on the pooled data from these trials (39). This pooled analysis represents the largest tocolytic trial performed to date. A total of 742 women diagnosed with preterm labor, using a strict inclusion and exclusion criteria, were enrolled to receive either atosiban or a β-agonist. The main outcomes of interest were effectiveness, which was defined as the number of women remaining undelivered after 48 h and 7 days of starting treatment, and a composite efficacy and tolerability end-point, which assessed the number of women remaining undelivered and not requiring alternative tocolysis. Atosiban was shown to be at least as effective as the β-agonists after 48 h and 7 days. In terms of efficacy and tolerability, significantly more women in the atosiban-treated group remained undelivered after 7 days and did not require alternative tocolytic therapy compared with the β-agonists (59.7% vs. 47.4%; $p = 0.0003$, see Fig. 3).

Secondary outcomes, such as mean gestational age at delivery and mean birthweight, were comparable. Regarding safety, atosiban demonstrated significant benefits over the β-agonists, with particular emphasis on maternal cardiovascular adverse events. There were significantly more cardiovascular events reported in the β-agonist group (81.2%) compared with the atosiban group (8.3%; $p < 0.001$). This was demonstrated by the fact that a significantly greater number of women discontinued treatment in the β-agonists group (15.4%) compared with the atosiban group (1.1%; $p = 0.0001$). In addition, clinically serious adverse events were reported in the β-agonist group, including two cases of pulmonary edema and one of myocardial ischemia (see Table I).

Fetal safety was comparable between the treat-

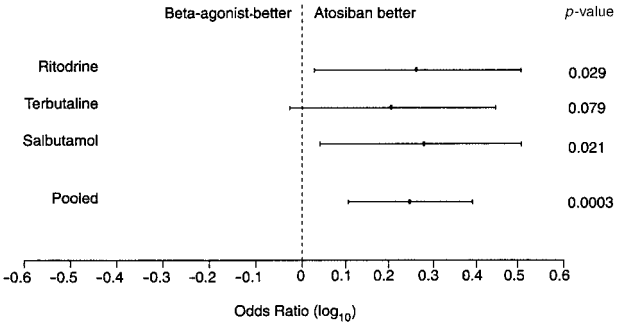

Fig. 3. Center stratified $\log_{10}$ odds ratio figure for the proportion of women undelivered and not requiring alternative tocolysis after 7 days of starting treatment in the three β-agonist trials and the pooled analysis. Figure reproduced from [39] with kind permission from Elsevier Science.

Table I. Frequency of maternal side-effects among treated enrolled women according to treatment allocation. Data reproduced from [39]

	Atosiban ($n = 361$)	β-agonist ($n = 372$)
Pulmonary edema	1 (0.3)*	2 (0.5)
Myocardial ischemia	0	1 (0.3)
Chest pain	4 (1.1)	18 (4.8)
Palpitation	8 (2.2)	58 (6.15)
Tachycardia	20 (5.5)	281 (75 5)
Hypotension	12 (3.3)	21 (52 7)
Dyspnea	1 (0.3)	27 (3.7)
Syncope	2 (0.6)	2 (0.5)
Nausea	43 (9.11)	59 (9.15)
Vomiting	25 (6.9)	81 (8.21)
Headache	35 (7.9)	69 (6.18)
Anxiety	4 (1.1)	11 (3.0)
Tremor	5 (1.4)	59 (9.15)
Hyperglycemia	23 (4.6)	46 (4.12)
Hyperkalemia	3 (0.8)	24 (5.6)

*Patient developed symptoms after rescue therapy with β-agonist.

ment groups although there were marked benefits for atosiban compared with β-agonists regarding tachycardia (3 vs. 28%, respectively). Neonatal outcomes were comparable between the treatment groups.

On the basis of the phase II and III study results, atosiban was introduced as the first licensed tocolytic, specifically developed for the treatment of preterm labor (the β-agonists were initially developed to treat asthma and gained a registration for the treatment of preterm labor because at the time there was a lack of safer alternatives).

Clinical experience with atosiban at the Vienna Medical School

Clinical experience with atosiban, outside the confines of a clinical trial design, provides a valuable insight into the acceptability of the drug to clinicians, nurses and patients.

A retrospective analysis of 83 women with threatened preterm delivery were treated with atosiban (40). Of these 83 women, 50 were in preterm labor, 21 had preterm premature rupture of the membranes (PPROM), six had vaginal bleeding, and a further six were diagnosed with an incompetent cervix. Gestational ages were between the 21st and 33rd week of pregnancy. At least two criteria had to be fulfilled before a positive diagnosis of preterm labor was made: regular uterine contractions (≥ 4 per 30 min) and one of either cervical length < 30 mm (examined by ultrasound) or a positive fetal fibronectin test. The majority of patients had a gestational age and birthweight at delivery to suggest that the inclusion/exclusion criteria used for the diagnosis of preterm labor was reliable.

Atosiban was administered according to the standard regimen i.e. initial bolus (0.9 ml injection of 6.75 mg over a minute) followed by a high-dose saturation infusion (18 mg/h over 3 h) and then a reduced infusion (6 mg/h over 45 h).

Outcome parameters were the same as the pooled analysis i.e. tocolytic effectiveness represented the number of women remaining undelivered after 48 h and 7 days. The frequency of contractions before and 3–12 h after starting treatment was also assessed. Safety was assessed in terms of maternal side-effects, perinatal and neonatal morbidity.

After 48 h, 85.4% of women remained undelivered and, after 7 days, there were still 72.5% of women who remained undelivered (Fig. 4). In addition, there was a dramatic reduction in the mean number of contractions from 8.0 ± 4.9 before treatment to 2.4 ± 3.2 every 30 min.

In terms of safety, the only side-effects that were associated with the administration of atosiban were minor and related to the initial bolus dose. The duration of these side-effects, which included nausea, flushing and vertigo, was brief, lasting for only 1–2 min. During the infusion period, only 6% of patients experienced minor side-effects, which were probably related to the study drug. Perinatal and neonatal outcome was similar to those results from children treated with other tocolytics.

In women with PPROM, 52.6% experienced a prolongation in pregnancy for 7 days. In terms of the mean number of days until delivery, atosiban prolonged pregnancy for 35 days in women with preterm labor while women with PPROM had a delay of 11 days.

To summarize, atosiban was shown to be com-

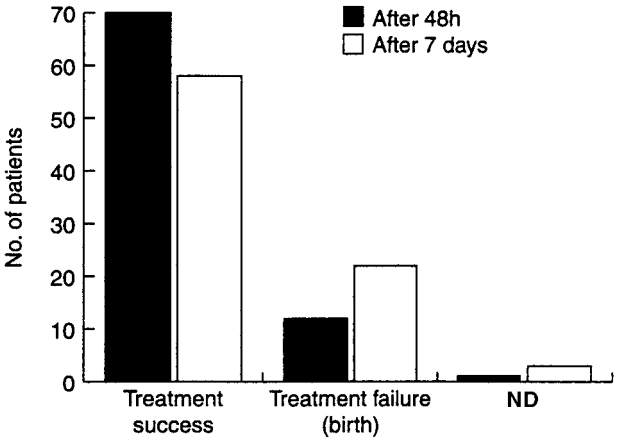

Fig. 4. Tocolytic success at 24 h and 7 days following atosiban administration. Figure adapted from data from [40].

parable to the β-agonists in terms of delaying delivery, and was also effective in women with PPROM who would normally be contraindicated for treatment. Atosiban represents a much safer alternative to the β-agonists, with only minor, transient maternal side-effects occurring during the initial bolus dose. Future investigations are underway in a phase IV 'TREASURE' trial (TRactocile Efficacy Assessment SURvey in Europe), which will continue to monitor and evaluate the efficacy and safety of atosiban in the clinical setting. It is intended that atosiban will be compared with currently used tocolytics, and, furthermore, the impact of early vs. deferred atosiban treatment will be investigated in women not yet eligible for treatment in order to explore the potential benefits of using atosiban outside the current recommendations.

Discussion

The introduction of atosiban into the clinical setting provides the opportunity to change the way preterm labor is managed. In the past, the mother was often overlooked as side-effects were considered unavoidable in many cases. As such, the current rationale of when to administer tocolysis is very much based on a risk/benefit approach: with treatment being provided in clinical situations where the risk to the mother and baby is outweighed by the potential benefit expected by keeping the baby *in utero*. In current clinical practice, the mother usually requires careful assessment before and during administration of conventional tocolytics. However, when a woman presents with threatened preterm delivery, tocolysis needs to be administered within a short period of time. Therefore, there is little time to carry out assessments of clinical parameters, such as fluid balance, to ensure the patient is suitable for tocolysis. Similarly, one of the principle reasons for the limited exposure of tocolytics in the clinical setting, normally for up to 48 h, is because of the side-effects of conventional agents. Nevertheless, the 48-h delay provides a significant contribution to neonatal outcome because it is used to transfer the mother *in utero* to a neonatal intensive care unit where corticosteroid treatment can be administered for fetal lung maturation.

At later gestational ages beyond 30 weeks, many clinicians would not consider exposing the mother to unnecessary side-effects especially as the incremental benefits to the fetus begin to diminish. However, a tocolytic agent that does not present a risk to the mother or her baby offers the potential to treat for longer periods and at later gestational ages to maximize fetal development. Furthermore, because atosiban does not exhibit a tolerability threshold, this increases the ability to continue administering the drug over a prolonged period until the desired outcome is reached. Importantly, unlike the β-agonists, atosiban is not associated with tachyphylaxis. Prolonged administration of β-agonists eventually leads to a decreased response as a result of the reduced number of receptors. In order to achieve the same response, a higher dose is subsequently required, increasing the potential for side-effects.

Another important issue concerns the medico-legal implications of using a nonlicensed tocolytic if a patient experiences serious side-effects. To minimize the risk of legal action, the use of the safest available tocolytic agent should be advocated.

Initial experience with atosiban in the everyday clinical setting has been very encouraging, particularly with the low incidence of side-effects encountered. Only minor side-effects were reported, which soon dissipated after completing the administration of the bolus dose. Another interesting observation from the retrospective analysis was the degree of success in women with PPROM. The use of tocolysis in women diagnosed with PPROM is controversial because prolonging pregnancy is associated with an increased risk of infection to the mother and baby. Although there have been several studies that have investigated the use of tocolysis in women with PPROM, as a result of the small numbers involved they were unable to justify the use of tocolysis (41). However, the evidence gained from clinical experience at the Vienna Medical School is encouraging, with significant prolongation in delivery, and no complications observed. As long as there are no maternal or fetal complications, it may be appropriate to prolong pregnancy in women with PPROM. However, it is important to ascertain the expected benefit vs. immediate delivery as PPROM is associated with increased infection, hence such a decision will also be heavily influenced by the gestational age. Management of PPROM could include the prophylactic use of atosiban together with antibiotics for up to 34 gestational weeks.

Atosiban is the first tocolytic to be introduced for over 20 years, and was developed specifically for the treatment of preterm labor. This explains its favorable safety profile compared with the conventional tocolytics that are available. The results from the forthcoming TREASURE trial should help to further elucidate the benefits offered by atosiban in the everyday clinical setting. For the first time obstetricians are presented with the opportunity to change the way that they manage preterm labor which, depending on the TREASURE

results, may lead to real improvements in neonatal outcome.

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