An overview of the efficacy and safety of novel erythropoiesis stimulating protein (NESP)

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Abstract

Novel erythropoiesis stimulating protein (NESP, also known as darbepoetin alfa) is a molecule that stimulates erythropoiesis by the same mechanism as both native and recombinant human erythropoietin (rHuEPO). The extra sialic residues on NESP, however, allow it to be more stable in vivo with a 2- to 3-fold longer elimination half-life. Thus, following intravenous administration, the mean elimination half-life of NESP is 25.3 vs 8.5 h for rHuEPO. After subcutaneous administration, the mean terminal half-life for NESP is 48.8 h. The mean bioavailability of NESP after subcutaneous administration is ~37%, similar to that reported for rHuEPO. The pharmacokinetic data suggested that patients with renal anaemia would require less frequent dosing with NESP than with rHuEPO. NESP 0.45 µg/kg administered once weekly either intravenously or subcutaneously has been evaluated for the correction of chronic renal failure (CRF)-associated anaemia. The study population included CRF patients not receiving dialysis, along with those on haemodialysis or peritoneal dialysis. In patients who are rHuEPO-naïve, NESP has a similar effect in correcting the anaemia as is seen with rHuEPO, but with less frequent dosing. Similarly, in patients previously receiving rHuEPO, NESP (whether administered intravenously or subcutaneously) is as effective as rHuEPO treatment for maintaining haemoglobin concentration when administered at a reduced frequency (i.e. either once weekly or once every other week). NESP is well tolerated, adverse effects are similar to those seen with rHuEPO, and no antibodies have been detected in >1500 patients exposed to NESP thus far.

Keywords: anaemia; chronic renal failure; dialysis; dosing frequency; haemoglobin; NESP

Introduction

The management of renal and other anaemias has been transformed over the last decade by the introduction of recombinant human erythropoietin (rHuEPO) therapy [1–4]. Over this period, rHuEPO has become widely accepted as an effective and well tolerated treatment, and its clinical benefits in patients with chronic renal failure (CRF) are well documented [5]. rHuEPO is administered by subcutaneous or intravenous injection and, due to its relatively short circulating half-life, it has generally been given two or three times a week [3,5–7]. Novel erythropoiesis stimulating protein (NESP, darbepoetin alfa) is an erythropoietic agent that has been shown to have a 3-fold longer terminal elimination half-life in both animal models [8] and humans [9] compared with rHuEPO. This created the potential for once weekly dosing to treat renal anaemia both in dialysis patients [10] and in those with chronic renal insufficiency (CRI) not yet requiring dialysis [11].

In the clinical development programme for NESP in the nephrological setting, >1500 patients have received the drug. This has involved 13 studies conducted across Europe, Australia, Canada and the USA. These studies have examined the pharmacokinetics of NESP (with both single and multiple dosing), along with its clinical efficacy and safety in patients with CRF. The aim of this article is to summarize the available data on the early clinical use of this new agent. Since there are important differences in molecular structure between NESP and rHuEPO that affect its biological activity in vivo, the clinical use of NESP differs in a number of respects from rHuEPO, and is discussed elsewhere in this supplement (pp. 22–27) [12].

Pharmacokinetic profile of NESP

The metabolic fate of both endogenous erythropoietin (EPO) and rHuEPO remains poorly understood. Renal elimination is minimal, and it is thought that
the hormone is desialated and cleared via galactose receptors in the liver [13]. It is the sialic acid residues on the EPO molecule that maintain its biological activity in vivo [14], and desialated EPO is rapidly cleared from the circulation. Pharmacokinetic analyses in both animal models and in humans have shown that, as a result of its increased sialic acid content, the serum half-life of NESP is approximately 2- to 3-fold longer than for rHuEPO.

In peritoneal dialysis (PD) patients, the mean terminal elimination half-life following a single dose of intravenous NESP was 25.3 h, three times longer than for intravenous rHuEPO (8.5 h) (Figure 1). After subcutaneous administration, the mean terminal elimination half-life for NESP was 48.8 h, which was twice as long as that for intravenous NESP (Table 1). This difference reflects the fact that the elimination half-life after subcutaneous administration is determined not only by its elimination from the central (blood) compartment, but also by continued slow absorption into the circulation from the subcutaneous injection site. The mean bioavailability of NESP is 36.9% [9], similar to that reported for subcutaneous rHuEPO [9,15,16]. The area under the serum concentration–time curve is significantly greater for NESP, and clearance is lower compared with similar doses of rHuEPO. The volume of distribution for NESP is similar to that of rHuEPO (52.4 vs 48.7 ml/kg) and is approximately equivalent to plasma volume.

The pharmacokinetics of NESP have also been determined following chronic intravenous [17] and subcutaneous [18] administration. Intravenous NESP was administered three times a week or once a week and compared with intravenous rHuEPO given three times weekly. As with the previous single-dose studies, the elimination half-life of NESP was found to be ca. 3-fold longer than for rHuEPO. Moreover, the pharmacokinetics of chronic intravenous therapy was both dose- and time-linear, and there was no evidence of accumulation for either three times weekly or once weekly NESP dosing regimens over 48 weeks of treatment [17].

In 16 patients scheduled to receive subcutaneous NESP once weekly, the pharmacokinetic profile was also investigated over 7 days during week 1 and week 8 of a long-term maintenance study, in order to evaluate dose- and time-dependency of pharmacokinetic parameters and accumulation. The results suggested that there was no evidence of dose- or time-dependence with chronic subcutaneous administration, and no accumulation of NESP over time [18].

The disposition of NESP has been evaluated in a small number (n = 12) of paediatric patients [19]. Following both intravenous and subcutaneous NESP administration, the pharmacokinetics were similar in both adult and paediatric patients with CRF. However, a comparison of the time to maximum serum concentrations following subcutaneous administration suggests that NESP may be absorbed more rapidly in paediatric patients, (mean 36.2 h in children

Table 1. Mean pharmacokinetic parameters of NESP following intravenous and subcutaneous administration [9]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intravenous NESP</th>
<th>Subcutaneous NESP</th>
</tr>
</thead>
<tbody>
<tr>
<td>t_{1/2a} (h)</td>
<td>25.3</td>
<td>48.8</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>–</td>
<td>54.1</td>
</tr>
<tr>
<td>C_{max} (mg/l)</td>
<td>–</td>
<td>0.94</td>
</tr>
<tr>
<td>AUC (mg . h.l)*</td>
<td>291.0</td>
<td>108.2</td>
</tr>
<tr>
<td>Clearance (ml.h/kg)</td>
<td>1.6</td>
<td>–</td>
</tr>
<tr>
<td>V_{ss} (ml/kg)</td>
<td>52.4</td>
<td>–</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>–</td>
<td>36.9</td>
</tr>
</tbody>
</table>

t_{1/2a}, terminal phase elimination half-life; T_{max}, time to maximum serum concentration; C_{max}, maximum serum concentration; AUC, area under serum concentration–time curve; V_{ss}, volume of distribution at steady state.

* AUC_{0-0.96} intravenous; AUC_{0-2} subcutaneous.
vs 54.1 h in adults). This is similar to that observed with rHuEPO [20].

Therapeutic trials of NESP in renal anaemia

The clinical programme for NESP has included studies that have examined the efficacy and safety in three phases of renal anaemia management: correction, conversion from rHuEPO to NESP, and long-term maintenance of haemoglobin concentrations. Correction studies investigated the effect of NESP in treating anaemia in CRF patients who have not previously received rHuEPO (rHuEPO-naïve). Conversion studies assessed the ability of NESP to maintain stable haemoglobin levels in patients whose anaemia had already been successfully treated with rHuEPO. Maintenance studies investigated the capacity of NESP to maintain haemoglobin concentrations effectively and safely in patients treated for periods of up to 12 months.

Correction of anaemia with NESP

Two multicentre studies investigated the optimal dosing schedule of NESP for the correction of anaemia in haemodialysis (HD) patients and PD patients. The study designs were very similar: one study involving HD patients treated with intravenous NESP, and the other involving PD patients receiving subcutaneous NESP. Both studies were conducted using an open-label dose-escalation protocol, and patients received NESP either once weekly in a dose range of 0.075–0.75 µg/kg, or three times weekly over a dose range of 0.025–0.25 µg/kg [21]. Thus, patients in both studies received the same total weekly dose, and the primary endpoint was the rise in haemoglobin over the first 4 weeks. There was a dose-dependent increase in haemoglobin in both studies (Figure 2), with no apparent difference between once and three times weekly dosing with NESP. NESP doses of 0.45 and 0.75 µg/kg/week provided optimal responses in 60–70% of patients (defined as a haemoglobin increase of 1–3 g/dl over the first 4 weeks). With the lower doses, fewer than 25% of patients showed a >1 g/dl/month rise in haemoglobin. These results indicated a clear dose-related erythropoietic response to NESP over the initial 4 weeks of treatment. This did not appear to be influenced by the dosing schedule. The data suggested that an appropriate starting dose for NESP in the treatment of anaemia in dialysis patients is 0.45–0.75 µg/kg administered intravenously or subcutaneously once weekly. Importantly, at these doses, the increases in haemoglobin concentration were in line with the European Best Practice Guidelines (EBPG) for the management of anaemia in patients with CRF [5], which recommend a haemoglobin rise of 1–2 g/dl per month for rHuEPO therapy.

In the light of the results from these early dose-finding studies, two further studies were undertaken to evaluate the efficacy and safety of NESP for the correction of anaemia in both CRF [11] and dialysis [22] patients. The dose of NESP in these studies was selected to be 0.45 µg/kg/week. The primary endpoint was the proportion of patients achieving a ‘haemoglobin response’. Two criteria were used to define such a response: a rise in haemoglobin of ≥1 g/dl and an absolute haemoglobin level of ≥11 g/dl following treatment. Patients were included in the CRF study if they were anaemic (haemoglobin < 11 g/dl), had a creatinine clearance < 30 ml/min, and were not yet on dialysis. One hundred and sixty-six patients were recruited to the study, of whom 129 received subcutaneous NESP 0.45 µg/kg once weekly, and of whom 37 received subcutaneous rHuEPO 50 IU/kg twice weekly, which is ca. 10% higher than the total weekly dose of NESP.

![Fig. 2. Mean rate of rise (ROR) in haemoglobin (Hb) concentration (95% confidence interval [CI]) over the first 4 weeks of subcutaneous (SC) (▲) and intravenous (IV) (●) NESP treatment.](image-url)
The proportion of patients who achieved a haemoglobin response was similar in the two treatment groups (93% NESP, 92% rHuEPO). The mean rise in haemoglobin after 4 weeks of treatment was also similar: 1.38 g/dl NESP and 1.40 g/dl rHuEPO. The median time to achieve a haemoglobin response was 7 weeks (range 3–25 weeks) in both groups (Figure 3), and no patients required a change in the frequency of study drug administration. At the time of the haemoglobin response, the median weekly dose was 0.46 µg/kg for NESP and 100 IU/kg for rHuEPO [11].

In a further study, the efficacy and safety of NESP for the treatment of anaemia in rHuEPO-naive patients with CRF receiving dialysis (HD or PD) was evaluated. Out of 122 randomized patients, 91 received intravenous or subcutaneous NESP 0.45 µg/kg once weekly (approximately equivalent to 90 IU/kg of rHuEPO weekly based on peptide mass), and 31 patients received intravenous or subcutaneous rHuEPO 50 IU/kg three times weekly (150 IU/kg total weekly dose) [22]. Dose adjustments were performed as necessary to achieve a haemoglobin response, defined as a haemoglobin rise of ≥1 g/dl, and an absolute haemoglobin of ≥11.0 g/dl. The mean increase in haemoglobin over the initial 4 weeks of treatment was 1.10 g/dl in patients receiving NESP and 1.33 g/dl in patients receiving rHuEPO. By 20 weeks, the haemoglobin concentrations in both treatment groups were within the range 11–13 g/dl (Figure 4). In addition, the mean time to achieve a haemoglobin response was 10 weeks with NESP and 8 weeks with rHuEPO. The slightly slower haemoglobin response most likely reflects the 40% lower starting dose in the NESP group compared with the rHuEPO group on a protein mass basis. At week 20, the median weekly dose was 0.56 µg/kg for NESP and 156 IU/kg for rHuEPO.

Conversion of patients from rHuEPO to NESP therapy

Two studies have been undertaken to determine whether NESP is as effective and safe in maintaining haemoglobin levels when administered at a reduced dosing frequency compared with rHuEPO [23,24]. Patients successfully maintained on rHuEPO treatment were eligible for these studies. The objective was to show that haemoglobin concentrations could be maintained after conversion to NESP at a reduced dosing frequency. The primary endpoint for these studies was the change in haemoglobin between the baseline period on rHuEPO treatment and the evaluation period (i.e. following 20–24 weeks of NESP therapy). In the North American double-blind trial [23] and in the European/Australian trial [24], patients were clinically stable and had a haemoglobin concentration of 9.5–12.5 g/dl during a 4 week screening and baseline period. Patients were then randomized to NESP or rHuEPO, with the NESP-treated patients switching to an equivalent weekly dose but with a reduced frequency of administration, and the rHuEPO-treated patients continuing with the same dose and frequency of administration. The dose of NESP for each patient was calculated using a formula to equate the protein mass of the two molecules: 1 µg NESP = 200 IU rHuEPO. The route of administration remained the same.

In the North American double-blind study, a total of 507 HD patients were randomized (in a ratio of 1:2) to receive either intravenous NESP once weekly plus placebo twice weekly, or to continue on intravenous rHuEPO three times weekly [23]. The mean haemoglobin remained stable in both treatment groups from baseline to the evaluation period (Figure 5). The mean change in haemoglobin level between baseline and the evaluation period (weeks 21–28) was 0.16 g/dl for

![Graph](image_url)

Fig. 3. Mean haemoglobin (Hb; 95% CI) over the first 16 weeks of NESP (▲, n=129) and rHuEPO (●, n=37) treatment in pre-dialysis patients.
NESP and 0.00 g/dl for rHuEPO. The between group difference in the mean change in haemoglobin concentration from baseline and evaluation was 0.16 g/dl. This was not a statistically significant or clinically relevant difference.

Thirty-one centres participated in the European/Australian study [24]. Eligible patients were those receiving regular dialysis (either HD or PD) and either intravenous or subcutaneous rHuEPO therapy. Patients on twice- or thrice-weekly rHuEPO converted to once weekly NESP. Patients on once weekly rHuEPO converted to NESP once every 2 weeks. In total, 522 patients were randomized, with 347 on NESP and 175 on rHuEPO (2:1 ratio). The mean haemoglobin remained stable from the baseline to the evaluation period for both treatment groups, with a change in haemoglobin of $-0.03$ g/dl for NESP and $-0.06$ g/dl for rHuEPO (Figure 6). The between-group difference in the mean change in haemoglobin concentration from baseline and evaluation was 0.03 g/dl. The difference was not statistically significant or clinically relevant. At the end of the evaluation period (weeks 24–32), 97% of NESP patients assigned to once weekly dosing and 95% of patients assigned to once every other week dosing were successfully managed at these reduced dose frequencies. The maintenance of haemoglobin concentrations, weekly dose requirements, and the frequency of dose changes in the NESP and rHuEPO groups were similar regardless of route of administration, even among NESP patients dosed once every other week.

Evaluation of dosing by route of administration in patients who received NESP or rHuEPO revealed that NESP dosing was similar for both the intravenous and subcutaneous route of administration over the course of the study. In contrast, dosing with rHuEPO was on average 22% lower by the subcutaneous route compared with the intravenous route.

The conclusion from both these studies was that NESP is as effective as rHuEPO for maintaining patients haemoglobin levels, but with less frequent dosing.

**Fig. 4.** Correction of anaemia with NESP ($\Delta$, $n=70$) and rHuEPO (●, $n=22$) in dialysis patients.

**Fig. 5.** Stability of haemoglobin concentrations NESP (—, $n=121$) and rHuEPO (−, $n=240$) patients in a double-blind, North American multicentre study. The $n$ values represent subjects completing the study per protocol.
**NESP for maintenance of haemoglobin levels**

An open-label study conducted in Europe and Australia evaluated the ability of NESP to safely maintain haemoglobin levels over a treatment period of up to 1 year [18]. Seven-hundred-and-three patients on HD or PD with a baseline haemoglobin level of between 9.5 and 12.5 g/dl were switched from rHuEPO to NESP therapy. In patients receiving rHuEPO once weekly (n=157), the frequency of NESP was reduced to once every other week. In patients receiving rHuEPO twice (n=203) or three times (n=343) weekly, the frequency on NESP was reduced to once weekly. Patients received NESP by the same route of administration at an initial equivalent dose to rHuEPO based on peptide mass (200 IU rHuEPO=1 µg NESP). The NESP dosage was titrated to maintain the haemoglobin within −1.0 and +1.5 g/dl of the patient’s baseline haemoglobin, and within a range of 9.0–13.0 g/dl. The mean change in haemoglobin from baseline to week 36 was 0.08 g/dl. This difference was neither statistically significant nor clinically relevant. The median weekly doses of NESP on study were equivalent to the weekly dose of rHuEPO at study enrolment, and 96% of patients were managed at the reduced dosage frequency, including 89% (139/157) on once every other week dosing.

**Safety and tolerability of NESP**

After a decade of clinical use, rHuEPO has emerged as a very well tolerated treatment for the vast majority of CRF patients with anaemia. The safety and tolerability of NESP was evaluated based on an integrated safety database of >1500 CRF patients who had been treated for up to 24 months [10]. Data presented from controlled studies included 1578 patients who received NESP and 591 patients who received rHuEPO. The overall proportion of patients who discontinued treatment due to adverse events was 2% for NESP and 4% for rHuEPO.

Undesirable effects considered attributable to treatment with NESP included hypertension and vascular access thrombosis. However, in the integrated safety database, neither of these events was associated with the haemoglobin concentration (<12 vs >12 g/dl) or haemoglobin rate of rise (<1, 1 to <2, 2 to <3 and >3 g/dl haemoglobin per 4-week period). Injection site pain was reported as attributable to treatment in studies where NESP was administered subcutaneously. The injection site discomfort was generally mild and transient in nature, and occurred predominantly after the first injection.

The incidence of undesirable effects considered related to treatment with NESP from controlled clinical studies was: common undesirable effects (1–10%); application site (injection pain); cardiovascular effects (hypertension); CNS/peripheral nervous system (headache); and vascular disorders (vascular access thrombosis). All other adverse events were observed at the ≤1% level (uncommon or rare), the majority of which were mild to moderate in severity and were consistent with the co-morbidities expected in this patient population.

**Immunogenicity**

All patients in the NESP clinical trial programme were closely monitored for NESP (and rHuEPO) antibodies. To date, the total number of patients tested for antibodies to study drug for up to 2 years was 1534 for NESP and 572 for rHuEPO. No evidence of antibody formation to NESP has been detected thus far.

**Decline in haemoglobin following withdrawal of NESP**

The ability to control elevated haemoglobin by withholding treatment is important for patient

![Fig. 6. Stability of haemoglobin concentrations from baseline to the evaluation period in a European/Australian multicentre study. NESP (−, n=224) and rHuEPO (−−, n=112). The n values represent subjects completing the study per protocol.](image-url)
management. In CR1 patients and dialysis patients whose haemoglobin concentration reached >14 g/dl, cessation of treatment resulted in a progressive reduction in haemoglobin concentration at a similar rate for both NESP and rHuEPO (Figure 7).

**Discussion**

The data presented in this review enable several conclusions to be drawn regarding the clinical use of NESP in treating renal anaemia. In patients who are rHuEPO-naïve, NESP produces a similar improvement in haemoglobin concentration to that seen with rHuEPO. However, this effect can be achieved with less frequent dosing. In patients with a prior exposure to rHuEPO treatment, NESP (whether administered intravenously or subcutaneously) at a reduced frequency of dosing (either once weekly or once every other week) is at least as effective as rHuEPO treatment for maintaining haemoglobin concentrations.

For the correction of anaemia, a starting dose of NESP 0.45 μg/kg administered once weekly either intravenously or subcutaneously is effective in increasing haemoglobin levels. In the NESP clinical development programme, both the rise in haemoglobin and the target haemoglobin achieved were in accordance with the recommendations of the EBPG for the management of anaemia in patients with CRF [5].

After conversion of patients from rHuEPO to NESP therapy, NESP can maintain haemoglobin levels as effectively as rHuEPO with less frequent dosing. Using a dose conversion formula which equates the protein mass of the two molecules (200 IU rHuEPO = 1 μg NESP), patients receiving rHuEPO two or three times a week can be changed to NESP once weekly, and patients receiving once weekly rHuEPO can be converted to NESP dosing once every other week.

With rHuEPO therapy, the subcutaneous route allows lower dosage requirements [5], but there is no obvious dosing difference when NESP is given intravenously or subcutaneously. This may be due to the longer elimination half-life of the molecule compared with rHuEPO, particularly by the intravenous route. This may offer some advantage to HD patients who are currently receiving weekly subcutaneous injections, allowing them to switch to intravenous dosing of NESP without a reduction in dosing efficiency.

NESP has a very similar safety profile to rHuEPO and is well tolerated. The only adverse events consistently reported as being related to NESP were hypertension, vascular access thrombosis and injection site pain with subcutaneous dosing, and these are consistent with the known safety profile of rHuEPO. It is encouraging that no antibodies to NESP have been detected to date.

Currently, rHuEPO is a well established treatment for renal anaemia, but in most patients it is administered two or three times a week. NESP has been shown to be as effective as rHuEPO, with a similar safety profile, and with less frequent dosing. Further studies and longer-term follow-up of NESP-treated patients are required, but the evidence to date suggests that NESP has a part to play in the management of CRF patients with anaemia.

**References**


