Monitoring and Management of Avastin-Associated Proteinuria

This letter responds to your request for information on Avastin® (bevacizumab) and the monitoring and management of proteinuria. The information provided is focused on the safety of Avastin in licensed indications.

In Brief

- Refer to the local Avastin label for the incidence rates of proteinuria, and management strategies approved by relevant regulatory authorities.
- The mechanism of Avastin-associated proteinuria is unknown; however, VEGF inhibition may compromise the renal glomerular filtration barrier.
- Risk factors for developing proteinuria include a history of hypertension, and receiving high-dose Avastin. Several systematic reviews have identified other potential risk factors.
- Recommendations
  - Patients should be tested for proteinuria prior to the start of Avastin therapy.
  - Whilst there are no formal recommendations on the frequency of monitoring proteinuria during Avastin therapy, patients in Avastin pivotal trials were assessed at the start of every or every other treatment cycle.
  - AEs should be managed per local Avastin label.
- Several published guidelines describe strategies for the monitoring and management of Avastin-associated proteinuria.

Abbreviations

AE= Adverse event
EMA= European Medicines Agency
FDA= Food and Drug Administration
SPC= Summary of Product Characteristics
UPC= Urine protein creatinine
VEGF= Vascular endothelial growth factor

Mechanism of Avastin-associated proteinuria

Proteinuria is considered a class effect of anti-VEGF agents[1], such as Avastin. The mechanism of Avastin-associated proteinuria is unknown, though several hypotheses exist.

VEGF plays a pivotal role in maintaining the endothelial fenestrations and podocytes of the renal glomerular filtration barrier.[2] Inhibition of VEGF signaling is thought to lead to[1-3]

- loss of endothelial fenestrations,
- loss of podocytes, and
- glomerular thrombotic microangiopathy with endotheliosis.

This may result in the disruption of the glomerular filtration barrier and result in excess protein excretion in the urine.[1,4]

Proteinuria risk factors to consider

In clinical trials, proteinuria was reported within the range of 0.7% to 54.7% of patients receiving Avastin[5]. Risk factors for developing proteinuria with Avastin include

- history of hypertension, and
- receiving high-dose Avastin[5].

Several meta-analyses and retrospective analyses have additionally identified other proteinuria risk factors, though findings are not consistent between analyses. Other proposed risk factors include

- renal cell carcinoma[6]
- renal failure[7]
- history of diabetes,[8] and
- number of Avastin cycles[9]

Avastin-induced proteinuria is thought to be reversible, though long term effects are not known[10].

Evaluating renal function and proteinuria prior to Avastin initiation

Test for proteinuria prior to the start of Avastin therapy. Beyond this, Roche does not provide recommendations on how to test renal function prior to Avastin therapy, or renal function limits on when to initiate Avastin.

The decision whether to use Avastin in patients with proteinuria lies with the physician and should be based on an appropriate assessment of the likely risk:benefit ratio. If Avastin were to be prescribed in this condition, we would advise appropriate clinical caution and monitoring.

Assessment of baseline renal function in Avastin pivotal trials

Several assessments were used to catagorise renal function at enrolment of Avastin pivotal trials, including assessing serum creatinine levels, performing urine dipstick analysis and calculating UPC levels[11-18].

Patients with compromised renal function were excluded from pivotal Avastin clinical trials. In many pivotal trials, proteinuria was allowed at a low level[11-14], defined as urine dipstick proteinuria <2+.

Patients with ≥2+ proteinuria on dipstick urinalysis at baseline underwent 24 hours urine collection and must have demonstrated ≤1 g of protein/24 hr before they were allowed to be enroled.

- Please refer to individual Clinical Trial protocols for further details on renal inclusion criteria, as some clinical trials had more stringent criteria.

Monitoring proteinuria during Avastin treatment

Roche does not provide recommendations on the frequency of monitoring proteinuria during Avastin therapy[5]. General recommendations are available in certain local Avastin product labels:

- EMA SPC —[19] Test for proteinuria by dipstick urinalysis during Avastin therapy.
- FDA label — [20] Monitor for the development or worsening of proteinuria with serial urinalysis during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment, such as a 24-hour urine collection.

Monitoring of renal function in Avastin pivotal trials

In pivotal clinical trials, patients were monitoring for proteinuria every, or every other treatment cycle.[11-18]

Management of proteinuria during Avastin treatment[5]

Manage AEs as per local Avastin Label.

- Discontinue Avastin if nephritic syndrome (grade 4 proteinuria) arises.

Additional recommendations from the Avastin FDA label are outlined on Table 1.

Table 1: FDA label recommendations for proteinuria

If urinary protein is	Then
≥2 g/24 hr	withhold Avastin
<2 g/24 h	resume Avastin
Is there a proteinuria level associated with grade 4 proteinuria / nephrotic syndrome?	discontinue Avastin

Study protocols from pivotal clinical trials varied with regard to the evaluation of proteinuria and management of Avastin between the time of elevated dipstick urinalysis and 24-hour urine collection, though many[11,12,14] resembled the recommendations outlined in the FDA label.

Published guidelines

Several publications describe monitoring and management strategies for proteinuria in Avastin patients.[10,21,22] We refer the interested reader to the publications for more information.

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