**Effectiveness and predictors for response to somatostatin analogues in patients with severe gastrointestinal bleeding due to angiodysplasias: a pooled analysis of individual patient data**

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**Abstract**

Introduction: Cohort studies have shown a beneficial effect of octreotide in decreasing the rebleeding rates in patients with gastrointestinal angiodysplasias, however with large variation among individuals. Most studies have a small sample size and different primary outcomes, which makes it difficult to estimate the true effect on clinical relevant outcomes such as transfusion dependency and to investigate predictors for clinical response.

Aims & Methods: The aim of this individual patient data meta-analysis is to investigate effectiveness of somatostatin analogues (SSA) on transfusion dependency and identify subgroups of patients that benefit most from SSA. A systematic search up to February 2016 in MEDLINE, EMBASE and the Cochrane Library was performed to identify articles reporting the effect of SSA in gastrointestinal angiodyplasias. We collected individual patient data of included articles and assessed the risk of bias with the MINORS tool. Patients with only oral iron dependency or where the GI bleeding was of unknown cause were excluded. The primary outcome was response to SSA, defined as good: ≥ 50% reduction of red blood cell (RBC) transfusions; or poor: < 50% reduction of RBC transfusions. We used multivariate logistic regression to determine the effects of patient and disease characteristics on SSA. The variable “study” was included in the univariate analysis to correct for study-effect.

Results: We identified 9 studies and obtained individual data from 6 (n = 180) cohorts and aggregated data were available for another 2 studies (n=36). We analyzed data of 159 patients (mean age 70 years, 56% men) with transfusion dependency due to gastrointestinal angiodysplasia bleeding that were treated with SSA. Half of the patients had angiodysplasias at multiple sites. Octreotide LAR 20 mg was the most frequently used (81%). Side-effects occurred in 31% (41/131) of the patients, with gastrointestinal symptoms (19.8%) and erythema / pain at the injection site (8.4%) the most frequent. In 8 patients (6%) SSA was discontinued due to side-effects.

There was a high SSA response with 89% of the patients having >50% reduction of their parenteral iron and/or RBC transfusion dependency. Sex, age, small bowel and stomach localization, the use of anticoagulants , dose, only parenteral iron dependent and prior endoscopic treatment were not associated with treatment response. Univariate analyses showed angiodysplasia localization in the colon (OR 0.28, 95% CI 0.09-0.88, *p* = 0.03) and stomach (OR 0.4, 95% CI 0.1-1.1, *p* = 0.07), number of transfusions (OR 0.95, 95% CI 0.9-1.0, *p* = 0.12) and at multiple sites (OR 0.37, 95% CI 0.17-0.77, *p* < 0.01) were associated with a poor response. Multivariate analyses found the number of transfusions as only independent factor associated with treatment response (OR 0.91, 95% CI 0.8-0.99, *p* = 0.036).

Conclusions: Based on this pooled analysis of data from individual patients with transfusion dependent angiodysplasia bleeding, SSA is effective and safe in the majority of patients. A decreased SSA response is found in patients with severe transfusion dependency before initiating SSA.

**Key Words:** meta-analysis, somatostatin analogue, gastrointestinal angiodysplasias, transfusion

**List of abbreviations**

**AD** Angiodysplasia

**CI** Confidence interval

**Hb** Haemoglobin

**IDA** Iron deficiency anaemia

**IPD** Individual patient data

**OR** Odd’s ratio

**RBC** Red blood cell

**SSA** Somatostatin analogues

**SD** Standard deviation

**Introduction**

Gastrointestinal angiodysplasias (AD) are vascular malformations that consists of thin-walled, dilated communications between veins and capillaries that easily bleed, and thereby can lead to iron deficiency anaemia or overt bleeding (REF). Elderly patients frequently suffer from symptomatic disease that may range from mild chronic anaemia to severe transfusion dependency necessitating hospitalizations. The most effective treatment is endoscopic argon plasma coagulation with a clinical response rate up to 90% (REF). However, re-bleeding rates can be as high as 57% after one year (REF). Indeed, repeated rebleeds in elderly patients who have exhausted endoscopic therapy results in refractory anaemia. Repeated blood transfusion as an option to correct anaemia is intuitive. However, the dilemma is that clinical studies emphasize the paradox that both anaemia and transfusion are associated with unfavourable outcomes, including organ injury, cardiovascular events, lower quality of life, and increased morbidity and mortality across patient populations (REF anesthesie).

This has prompted the search for alternative strategies in AD patients who have become dependent on blood transfusions. Somatostatin analogues (SSA) have emerged as an attractive alternative treatment modality in severe bleeding AD. Mechanism of action is thought to be through decrease of splanchnic blood flow, enhancing platelet aggregation and its anti-angiogenic effect (REF). In particular, octreotide as the prototype somatostatin analogue has been studied in this condition. Small cohort studies have shown a beneficial effect of octreotide in decreasing the rebleeding rates and transfusion requirements in patients with gastrointestinal AD (REF). This lends credibility to the use of octreotide in endoscopic refractory AD but a well performed randomized controlled trial that supports its use has not been performed.

There are some important limitations inherent to the small sample size. The effect size of the efficacy of octreotide has not been established and it is not known whether there is a dose response relation. In addition, one study identified several factors that led to a poor response such as older age, male gender, presence of aortic stenosis, chronic antiplatelet therapy, chronic obstructive pulmonary disease and chronic renal failure (REF). Replication of these findings are still outstanding. Finally heterogeneity among studies precludes direct comparison and explaining heterogeneity with data on a study level is very difficult and does not relate effects of treatment to the individual patient (REF meta-analyse CGH). To overcome these limitations and increase statistical power, we performed an individual patient data (IPD) pooled analysis using data from six cohort studies.

We hypothesize that patient and AD characteristics affect the effectiveness of SSA and that there is a dose-response relationship. The aim of the current IPD pooled analysis is to estimate the effect of SSA on transfusion requirements in AD subgroups based on underlying treatment (i.e. doses), patient and AD characteristics to identify patients that benefit the most of SSA therapy.

**Methods**

Literature search

This study is performed according to the PRISMA-IPD statement (REF). We performed a systematic literature search in the following electronical databases: MEDLINE, Embase, the Cochrane Library and clinicaltrials.gov in January 2015, with an update on 14 November 2016. A clinical librarian assisted in creation of correct and complete search syntax. The search terms ‘angiodysplasia’ (synonyms: vascular malformation, angioectasia, ateriovenous malformation, ectasia, vascular lesion, vascular abnormality, vascular abnormalities or watermelon stomach) and ‘octreotide’ (synonyms: somatostatin, or sandostatin) were combined and Mesh terms were used (see appendix 1 for the search strategy).

Study selection

We included all original studies that were published as full articles that investigate the effect of SSA on transfusion requirements in patients with AD. AD had to be diagnosed by endoscopy, i.e: gastroduodenoscopy, colonoscopy, balloon assisted enteroscopy or videocapsule endoscopy. Studies including patients with a left ventricular assist device (LVAD) were excluded because of the very specific aetiology of bleeding. Moreover, conference abstracts, case-reports and cohort studies with less than 10 patients were excluded because of the selective reporting. Searches were not limited by language or time period. The search was completed by checking the references of all the selected studies to retrieve eligible studies possibly missed by our systematic literature search. To obtain the individual patient data the following strategy of contacting authors was used: 1. first authors, 2. last authors, 3. any co-author, 4. the department where the research was conducted, 5. retrieve correct contact information through the national gastrointestinal society of the country where the research was conducted, and 6. attending a conference where one of the authors was a speaker.

Data extraction

An electronic standardized form containing all variables with corresponding definitions was used to obtain data of the collaborators. One author (K.G.) who had not participated in any of the included studies, extracted, pooled and analysed all patient data. Subsequently, databases were checked for completeness and internal consistency and when appropriate corrections through correspondence with the collaborators were made. The quality and risk of bias is assessed using Methodological Index for Non-Randomized Studies (MINORS) quality assessment scale. This is a validated tool with 12 items that are scored as not reported (0 points), reported but inadequate (1 point) or reported and adequate (2 points). The global ideal score being 16 for non-comparative studies and 24 for comparative studies. The following domains were included for assessment of risk of bias: the selection of the study groups; appropriate study design and analysis; the comparability of the groups; and the ascertainment of outcome of interest. Authors were contacted for additional information in case the methodological quality of a study was not adequately described in the original article. Publication bias was assessed by funnel plots.

At the individual data level, patients were excluded with: no RBC transfusions in the year prior to initiating SSA, GI bleeding due to unknown cause and other causes then angiodysplasias (e.g. gastric antral vascular ectasias).

Outcomes

The primary outcome was response to treatment, defined as good: ≥ 50% reduction of red blood cell (RBC) transfusions; or poor: < 50% reduction of RBC transfusions in the first year of SSA treatment compared to the year prior to initiating SSA(REF). To give more insight on the primary outcome the mean percentual and absolute mean difference in number of red blood cell transfusions between the year prior to SSA treatment compared with the first year of SSA therapy are shown. Secondary outcomes are haemoglobin level and safety defined as the percentage of patients SSA treatment stopped due to adverse events (AEs) and tolerability, defined as the percentage of side-effects and AEs. Patient subgroups were based on patient characteristics (i.e. age at time of study inclusion, gender, comorbidities, use of anti-aggregation / anti-coagulantia), AD characteristics (i.e. location, extensiveness throughout the gastrointestinal tract) and treatment characteristics (i.e. doses).

Statistical analysis

Only studies of which actual data were obtained were used in the pooled analysis. Baseline characteristics of patients will be presented as mean (standard deviation (SD)) or median (interquartile range (IQR)) in case of non-normally distributed continues variables. Binary and categorical variables will be presented as frequencies and percentages. In case of missing values multiple imputation methods will be performed when the conditions for imputation are met. In the primary pooled analysis overall treatment effect of SSA will be assessed by descriptive statistics of the number of responders, partial- and non-responders. To compare the transfusion requirements and haemoglobin level between the year prior of treatment and treatment a paired two-sided students t-test or Mann Whitney U test will be used. Multinomial logistic regression analysis will be performed to identify predictors (e.g. dose, anti-coagulantia use, age) for a response to SSA therapy. Outcomes will be displayed as Odd’s ratios (OR) with 95%-confidence intervals (95%-CI).

As last, a sensitivity analyses will be performed to assess the effect of the studies where no individual patient data was obtained. The result of our analyses can be combined with subtracted data from the included studies in the pooled analysis. All statistical analyses are performed with SPSS statistical software package version 20.0 (SPSS Inc., Chicago, IL). All P values calculated were 2-tailed, and the level of significance was set at a α = .05.

Role of funding source

This study was not supported by any third party. The costs were fully covered by the authors’ institution.

**Results**

Study selection and IPD obtained

The initial search yielded 248 articles, resulting in 180 unique publications for title and abstract screening (Flow Diagram 1). After applying the inclusion- and exclusion-criteria 8 eligible articles and abstracts were retrieved. With hand-searching one additional article was found which was not indexed in the used search databases. In total we sought IPD of 9 studies and were successful in obtaining the data of 6 of these studies (n = 179). The IPD was not available of 3 studies (n = 68). We were unable to contact the authors (n=19) and data were destroyed (n=17) (REF), however of these studies the subtracted individual data were available from the published manuscript (n=36). For the last study (n=32), we extensively tried to get in contact with the authors, but we stopped our attempts after it became clear that the principal investigators retired and data were probably deleted (REF).

Individual patients were excluded in the merged database due to no RBC transfusions in the year prior to initiating SSA (n = 37), unknown cause of GI bleeding (n=2) and GAVE (n=5).

Study characteristics

All 9 cohort studies (n=245) investigate the effect of SSA in patients with transfusion dependency due to proven gastrointestinal AD. The sample size per study was relatively small (range 11-32), except for one study with 98 participants. The non-available study is the only study with an (external) control group, and together with the study of Nardone et al. (1999) uses short-acting octreotide. The median treatment duration ranges between 6-26 months with a follow-up period ranging from 13-78 months between studies. The primary endpoint in 5 studies was the percentage of responders, defined as no blood and iron transfusions during octreotide therapy. The other 2 included studies focussed on transfusion requirement, one study compares the average monthly transfusion rate and the other the decrease in blood transfusion requirements before and after starting SSA. One of the non-available study has failure of treatment as primary endpoint, defined as the presence of any episode of acute gastrointestinal bleeding, or chronic gastrointestinal bleeding with positive fecal occult blood test and iron deficiency anaemia with hematocrit below 26% or hematocrit below 30% despite continuous iron therapy for 6 months.

Assessment of risk of bias within studies

The methodological quality assessed with the MINORS quality assessment tool was moderate with scores ranging from 7-15 in the 9 cohort studies (table 2). Most studies had a clear stated study aim and correct inclusion with all consecutive patients presenting in their hospital. Five studies were prospective with appropriate endpoints defined up front. There are no blinded studies and no sample size calculations performed. All studies had a minimum or median follow-up of > 1 year, except for one study which only report a 6 months follow-up. Only one study had a control group, however this was taken from another RCT. Half of the analyses were inadequate due to the lack of a paired test, which should have accounted for the dependent variations before and after treatment.

Funnel plots of the primary outcome showed.......

Baseline characteristics

We analyzed data of 174 patients (mean age 70 years, 55% men) with RBC transfusion dependency due to gastrointestinal angiodysplasia bleeding that were treated with SSA (table 3). Two-third of the patients uses a form or combination of blood thinners, with 38% using antiplatelet drugs and 41% anticoagulants. Almost half (48%) of the patients had angiodysplasias at multiple sites, with the small bowel as most frequent location (73%), and an equal distribution in colon (44%) and stomach (44%). Prior to starting SSA, endoscopic treatment with argon plasma coagulation was performed in 55%. Octreotide LAR 20 mg (64%) and 10 mg (26%) were prescribed in the majority of patients. At baseline, the median haemoglobin level was 7.0 g/dL (IQR 1.9) with a median number of RBC transfusions in the year prior to SSA treatment of 8.0 (IQR 13.4). The median follow-up of 15 months (IQR 27).

Results of primary outcome

Only 23 patients (13.4%) had a poor response to SSA treatment with a percentual decrease of <50% in RBC transfusions between the year prior to initiating SSA and the first treatment year. Over half of the patients (53.5%) had a full response with nil RBC transfusions during SSA treatment. There was a significant difference between number of RBC transfusions between the year prior to SSA and during SSA (13.0 vs. 2.9, *p*<0.001) (Figure 1). To correct for differences in baseline RBC transfusion requirements, the percentual decrease is shown in Figure 2. The mean decrease is 74% in number of RBC transfusions between prior year and first year of SSA therapy. The study of Klimova et al. has a very broad 95% CI, this is due to one patient who had an increase in RBC transfusions from 2.5 to 15 (i.e. 500% increase).

The one study not included in this analysis is of Junquera et al. Compared with the control group there was no significant difference in RBC transfusion requirements found with the patients receiving octreotide (resp. 0.7 vs. 1.1, *p* >0.05).

Results of secondary outcomes

Hemoglobin levels increased significantly during SSA therapy from a baseline level of 6.4 g/dL to 10.6 g/dL (*p*<0.001).

Side-effects occurred in 23.5% (31/132, missings n=42) of the patients, with most commonly gastrointestinal symptoms like diarrhoea, abdominal pain, flatulence (n = 15, 11.5%), and erythema / pain at the injection site (n=8, 6.2%). Cholelithiasis occurred in 3 patients (2.3%). In 9 patients (5.2%) SSA therapy was discontinued due to the following side-effects: splenic infarction (n=1), allergic skin reaction (n=1), diarrhoea (n=1), cholelithiasis (n=2), pain at the injection side (n=1), thrombocytopenia (n=1) and for unknown reasons (n=2).

Results of risk factor identification

Tabel “baseline” responder en non-responder, geslacht etc. Univariate en multivariate. Nog imputatie, bij missing VG? **Opnieuw doen voor 3 categorieen van responders!!!**

Risk of bias across studies

Representativeness of available studies…….(externe validiteit)

Sensitivity analyses

Eventueel sensitiviteits analyse voor verschillende follow-up en niet de keuze 1 jaar ervoor en 1 jaar erna. Prospectief vs. retrospectief. Wel / geen imputatie.

**Discussion**

Summary of main findings

Strengths and limitations –

junquera, regression to the mean, no control group (regression to the mean)

General interpretation in the context of other evidence

Duur van aanhoudend effect. Hier met name jaar voor en na behandeling, studie aanhalen met langste follow-up en daarbij nog effect.

Implications

Other advantages are the ease of use and its relative mild side-effect profile.

Thalidomide is a angiogenesis inhibitor that is found to be effective (REF), but has the drawback of the risk of irreversible side-effects like polyneuropathy (REF).

* Why colonic patients respond worse?

**References**

[Br J Anaesth.](http://www.ncbi.nlm.nih.gov/pubmed/?term=J.+Anaesth.+(2011)+107+(suppl+1)%3A+i41-i59.) 2011 Dec;107 Suppl 1:i41-59. doi: 10.1093/bja/aer350.

What is really dangerous: anaemia or transfusion?

[Shander A](http://www.ncbi.nlm.nih.gov/pubmed/?term=Shander%20A%5BAuthor%5D&cauthor=true&cauthor_uid=22156270)1, [Javidroozi M](http://www.ncbi.nlm.nih.gov/pubmed/?term=Javidroozi%20M%5BAuthor%5D&cauthor=true&cauthor_uid=22156270), [Ozawa S](http://www.ncbi.nlm.nih.gov/pubmed/?term=Ozawa%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22156270), [Hare GM](http://www.ncbi.nlm.nih.gov/pubmed/?term=Hare%20GM%5BAuthor%5D&cauthor=true&cauthor_uid=22156270).

**Appendix 1:**

**Search strategy (in MEDLINE):**

((((octreotide[Title/Abstract] OR somatostatin[Title/Abstract] OR somatostatine[Title/Abstract] OR sandostatine[Title/Abstract] OR sandostatin[Title/Abstract])) OR "Octreotide"[Mesh])) AND (((Angiodysplasias[Title/Abstract] OR angiodysplasia[Title/Abstract] OR vascular malformation[Title/Abstract] OR vascular malformations[Title/Abstract] OR arteriovenous malformation[Title/Abstract] OR arteriovenous malformations[Title/Abstract] OR angioectasia[Title/Abstract] OR angioectasias[Title/Abstract] OR vascular ectasia[Title/Abstract] OR vascular ectasias[Title/Abstract] OR vascular lesion[Title/Abstract] OR vascular lesions[Title/Abstract] OR vascular abnormalities[Title/Abstract] OR vascular abnormality[Title/Abstract] OR watermelon stomach[Title/Abstract] OR watermelon stomachs[Title/Abstract])) OR "Angiodysplasia"[Mesh])

**Flow Diagram 1.** Study selection and obtained IPD.

No. Studies identified through other sources: **1**

No. Studies identified through search: **248**

No. Studies after duplicates removed: **181**

No. Studies excluded: **172**

No original patient data: 22

Not about AD: 86

Case-reports: 24

Patients with LVAD’s: 3

Not about SSA treatment: 10

No. of patients <10: 14

Abstracts: 4

Animal studies: 8

No full-text available: 1

No. Studies screened for eligibility: **181**

No. Studies for which IPD were sought: **9**

Table 2. Methodological study quality assessment by the MINORS.

**Analyzed IPD data**

No. studies included in the analysis: **6**

No. participants in analysis: **138**

No. Patients excluded based on:

No RBC transfusions at baseline: **37**

Unknown cause OGIB: **2**

Other cause than AD bleeding: **5**

No. Studies for which subtracted individual data were available: **2**

Excluded study: no IPD in published data

No. patients excluded: **32**

**Analyzed individual subtracted data**

No. studies included in the analysis: **2**

No. participants in analysis: **36**

No. Studies for which IPD were not provided: **3**

Reason: unable to contact the authors and data not available anymore

No. patients: **68**

No. Studies for which IPD were provided: **6**

No. patients with available data: **182**

No. patients without available data: **0**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Study aim | Correct inclusion | Prospective study | Clear outcomes | Unbiased outcome assessment | Appropriate FU period | Loss to FU <5% | Adequate power calculation | Control group | Contemporary controls | Baseline equivalence | Adequate analyses | Score (0-24) |
| Holleran | + | + | + | + | - | +/- | +/- | - | - | NA | NA | +/- | 11 |
| Klímová | + | + | +/- | + | - | + | +/- | - | - | NA | NA | +/- | 11 |
| Salgueiro | + | + | +/- | + | - | + | - | - | - | NA | NA | +/- | 10 |
| Nardone2 | +/- | + | +/- | +/- | - | + | - | - | - | NA | NA | + | 8 |
| Bon | + | + | + | + | - | + | + | +/- | - | NA | NA | + | 15 |
| Molina | +/- | + | + | + | - | + | - | - | - | NA | NA | +/- | 10 |
| Scaglione | +/- | + | + | + | - | + | + | - | - | NA | NA | + | 13 |
| Junquera | + | + | + | + | - | + | +/- | +/- | + | +/- | +/- | +/- | 17 |
| Nardone1 | + | - | - | +/- | - | + | - | - | - | NA | NA | + | 7 |

FU, follow-up; NA, not applicable, 1, first publication 1999; 2, second publication 2014

-, not reported (0 points); +/-, reported but inadequate (1 point); + reported and adequate (2 points)

Table 3. Baseline characteristics of individual patient data and subtracted IPD data (n=174).

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | Characteristic | N (%) | Missings, N (%) |
| **Gender** | Men | 86 (55) | 18 (10) |
| **Age** |  | mean 70 years, SD 12 |  |
| **Multiple locations** |  | 75 (48) | 18 (10) |
| **Location** | Stomach | 69 (44) | 18 (10) |
|  | Small bowel | 114 (73) | 18 (10) |
|  | Colon | 69 (44) | 18 (10) |
| **Comorbidities** | CKD | 33 (34) | 78 (45) |
|  | Valvular heart disease | 25 (26) | 78 (45) |
| **Blood thinners** | Yes | 66 (66) | 74 (43) |
|  | Antiplatelet | 38 (38) | 74 (43) |
|  | Anticoagulantia | 41 (42) | 74 (43) |

**Figure 1.** Plot of the individual studies and combined IPD data with their absolute mean difference in RBC transfusions in the year before and after start of SSA treatment.



**Figure 2.** Plot of the individual studies and combined IPD data with the percentual decrease in RBC transfusions in the year before and after start of SSA treatment.