ABSTRACT
Objectives: Acquired severe aplastic anaemia is a rare and potentially fatal disease. The aim of this Cochrane review was to evaluate the effectiveness and adverse events of first-line allogeneic haematopoietic stem cell transplantation of human leucocyte antigen (HLA)-matched sibling donors compared with first-line immunosuppressive therapy.

Setting: Specialised stem cell transplantations units in primary care hospitals.

Participants: We included 302 participants with newly diagnosed acquired severe aplastic anaemia. The age ranged from early childhood to young adulthood. We excluded studies on participants with secondary aplastic anaemia.

Interventions: We included allogeneic haematopoietic stem cell transplantation as the test intervention harvested from any source of matched sibling donor and serving as a first-line therapy. We included immunosuppressive therapy as comparator with either antithymocyte/antilymphocyte globulin or ciclosporin or a combination of the two.

Primary and secondary outcome measures planned and finally measured: The primary outcome was overall mortality. Secondary outcomes were treatment-related mortality, graft failure, graft-versus-host disease, no response to immunosuppressive therapy, relapse after initial successful treatment, secondary clonal disease or malignancies, health-related quality of life and performance scores.

Results: We identified three prospective non-randomised controlled trials with a study design that was consistent with the principle of 'Mendelian randomisation' in allocating patients to treatment groups. All studies had a high risk of bias due to the study design and were conducted more than 15 years. The pooled HR for overall mortality for the donor group versus the no donor group was 0.95 (95% CI 0.43 to 2.12, p=0.90).

Conclusions: There are insufficient and biased data that do not allow any conclusion on the comparative effectiveness of matched sibling donor-haematopoietic stem cell transplantation and immunosuppressive therapy.

INTRODUCTION
Acquired severe aplastic anaemia (SAA) is a rare and potentially fatal disease which is characterised by hypopcellular bone marrow and pancytopenia; it mainly affects young adults. The estimated incidence rate of SAA ranges from 0.7 to 4.1 per million people...
This article is based on a Cochrane Systematic Review published in The Cochrane Library. Publication of this work is in agreement with the policy of The Cochrane Collaboration. While preparing this systematic review and meta-analysis, we endorsed the PRISMA statement, adhered to its principles and conformed to its checklist.

Study inclusion criteria
We included randomised controlled trials (RCTs) and prospective non-RCTs as long as the study design was consistent with the principle of ‘Mendelian randomisation’ in allocating patients to treatment groups. We required a minimum of 80% of relevant patients per group and we set a minimum sample size of five participants per group. We set no limits on language, year of publication or year of treatment. We included participants with newly diagnosed acquired SAA. We did not set any age limits for participants. We excluded studies on participants with secondary aplastic anaemia. We included HSCT as the test intervention harvested from any source of MSD and serving as a first-line therapy. That means, no other HSCT or IST has been offered to the patients before. We included IST as comparator with ciclosporin combined with ATG as the current mode of IST. To accommodate former modes of IST, we also included ciclosporin combined with ALG, ciclosporin alone, ATG alone and ALG. Other agents such as corticosteroids and androgens were not considered. The primary outcome was overall mortality. Secondary outcomes were treatment-related mortality, graft failure, graft-versus-host disease, no response to IST, relapse after initial successful treatment, secondary clonal disease or malignancies, health-related quality of life and performance scores.

Principle of ‘Mendelian randomisation’
There are ethical concerns around randomisation of patients with SAA to transplantation versus non-transplantation because the risk of early death is expected to be higher in the transplantation group than in the non-transplantation group. The reason is the potentially life-threatening graft-versus-host disease occurring only in the transplanted patients. Gray and Wheatley described the potential of ‘Mendelian randomisation’ to minimise bias when comparing MSD-HSCT with an alternative therapy. The base concept has been ascribed to Katan. ‘Mendelian randomisation’ means the view that nature itself has already ‘randomised’ the paternal and maternal part of a gene given that donor and recipient are siblings. Thus, ‘Mendelian randomisation’ by definition accepts only siblings as transplant donors and these sibling donors are required to have ‘identical’ or matched features of specific transplant-relevant HLA sites when compared with the transplant recipient. Therefore, patients with an HLA-matched sibling will be allocated to the MSD-HSCT group. On the other hand, patients with siblings that are not HLA compatible will be allocated to the IST group. The term ‘Mendelian randomisation’ refers to the fact that the genetic distribution of paternal and maternal alleles follows a random process and is determined before birth. This concept takes advantage of an instrumental variable for allocating the patients to
treatment groups and, at the same time, this variable is neither associated with the treatment nor associated with the outcome.

**Search strategy and selection of studies**

We conducted an electronic literature database search in MEDLINE (Ovid), EMBASE (Ovid), and Cochrane Library CENTRAL (Wiley) including articles published from inception to 22 April 2013. The corresponding search strategies are depicted in the original Cochrane Review.⁷ We retrieved all titles and abstracts by electronic searching and downloaded them to the reference management database EndNote Version X3.¹⁴ Two authors assessed the eligibility of retrieved papers independently. We considered studies written in languages other than English. We judged studies to be prospective if an explicit statement was reported or there were clues suggesting a prospective design (eg, prior approval of treatment and informed consent). We judged studies to be retrospective if an explicit statement was reported or it was implied by description that data were reviewed from an existing source. We regarded each of the following items as an indication of a retrospective design: registry reports and reviewing of medical records. We judged studies as consistent with the principle of ‘Mendelian randomisation’ if all transplant donors were clearly siblings and if the allocation of patients to treatment groups was not based on age. We regarded studies as not consistent with the principle of ‘Mendelian randomisation’ if age was not balanced between groups, indicating that age played a role in the group assignment. Example for imbalance: distribution of age categories was statistically not comparable (p value less than 0.05).

**Assessment of risk of bias in included studies**

Two review authors independently assessed the risk of bias in the included studies using six criteria. We have used four criteria from The Cochrane Collaboration’s tool for assessing risk of bias: blinding of outcome assessment, complete outcome data such as missing data, selective reporting such as not reporting prespecified outcomes and other sources of bias such as bias related to the specific study design and competing interest. We extended the Cochrane tool for assessing risk of bias with two additional criteria that are specific to the inclusion criteria for the present review and critical for confidence in results: comparable baseline characteristics and concurrent control. We applied The Cochrane Collaboration’s criteria for judging risk of bias.¹⁶

**Data synthesis**

One review author entered the data into Review Manager.¹⁷ Another review author checked the entered data. We synthesised data on mortality for the donor group (MSD-HSCT) versus the no donor group (IST) by using the HR for time-to-event data as the primary effect measure with a random-effects model. If the HR was not directly given in the publication, we estimated HRs according to methods proposed by Parmar et al and Tierney et al.¹⁹

**RESULTS**

**Search results**

We identified three non-randomised, prospective, parallel and controlled clinical trials (figure 1). Bayever et al and Gratwohl et al reported their results in a single original article, respectively. Führer et al reported five

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**Figure 1** Study flow (IST, first-line immunosuppressive therapy; MSD-HSCT, first-line allogeneic haematopoietic stem cell transplantation of bone marrow of HLA-matched sibling donors; ‘MR’, ‘Mendelian randomisation’; SAA, acquired severe aplastic anaemia.
publications including one original article, a follow-up article, one protocol and two abstracts. We did not identify any RCTs.

**Characteristics of included articles**

The main study, patients and interventions characteristics are shown in table 1. The patients were treated and observed between 1976 and 1997. Thus, the reported data were collected more than 15 years ago. Median follow-up was not reported. Median age, fraction of males and median days of time interval between diagnosis and begin of treatment were roughly comparable between the treatment groups within each study. The age ranged from early childhood to young adulthood. In the study by Führer et al, all patients were less than 17 years old by definition of the inclusion criteria. Bone marrow was used as the source for all transplants. All three included studies had a high risk of bias due to the study design (table 2). We judged a low risk of bias for blinding the assessment of overall mortality. Blinding or lack of blinding is not expected to make a difference concerning overall mortality. The authors of all included studies did not report that ‘Mendelian randomisation’ was planned and the authors did not report the size of the involved families. The authors did not report the numbers of siblings and the results of the individual genetic analyses.

**Effects of intervention**

The pooled HR estimate for overall mortality was 0.95 with a 95% CI of 0.43 to 2.12 (p=0.90; figure 2). According to the meta-analysis based on data from all three included studies, overall mortality was not statistically significantly different between MSD-HSCT and IST. Overall survival ranged from 47% to 84% in the MSD-HSCT group and from 45% to 87% in the IST group (table 3). The results for the secondary outcomes including treatment-related mortality after MSD-HSCT, graft failure after MSD-HSCT, graft-versus-host-disease (GVHD) after MSD-HSCT, no response to IST and relapse after IST are shown in table 4. With respect to secondary clonal disease or malignancies, Bayever et al reported one patient who developed T-cell lymphoma after MSD-HSCT and Führer et al reported four patients who developed acute myelogenous leukaemia after IST. Health-related quality of life questionnaires were not used in any of the included studies. Bayever et al reported that almost all evaluable patients in the MSD-HSCT group (92%) and less than half of the patients in the IST group had a Karnofsky Performance Status of higher than 70%.

**DISCUSSION**

**Interpretation of main results**

We identified three prospective, non-RCTs, including 302 participants; 121 received MSD-HSCT and 181 received IST. On the basis of these trials we found
insufficient evidence to clarify whether MSD-HSCT leads to better overall survival than IST. Overall survival ranged from 47% to 84% in the MSD-HSCT group and from 45% to 87% in the IST group and in a meta-analysis, overall mortality was not statistically significantly different between the treatment groups. Treatment-related mortality in the MSD-HSCT group was considerable ranging from 20% to 42%. The graft failure rate was variable and caused the death of 3% to 16% of transplanted patients. GVHD affected a quarter to a half of transplanted patients. More than half of the patients in one study did not respond to IST. Relapse affected up to one in eight patients after IST in one study. Secondary clonal disease or malignancies were detected rarely in both treatment groups. Marsh et al. estimated that allogeneic bone marrow transplantation from an HLA-identical sibling donor provides a 75–90% chance of long-term cure in patients younger than 40 years of age. Similarly, in a review of studies with younger patients, Guinan reported an overall survival between 75% and 95% at 3–5 years. Sangiolo et al. concluded that their data favours extending MSD-HSCT to patients older than 40 years of age who are without significant comorbidities. The results of the studies included in the present systematic review appear to roughly match the recent estimates reported by others.

Recent therapeutic improvement
Bacigalupo (2008) reported that the outcome has improved since 1996 for HSCT but not for IST. Peinemann et al. identified three studies that reported a statistically significant improvement of overall survival in the group of matched related donor transplants but not in the IST group. Several factors may have contributed to recent improvements in HSCT, such as detailed HLA-matching and less irradiation-based conditioning. The Third Consensus Conference on the treatment of aplastic anaemia agreed in 2010 that bone marrow should be used as the source of stem cells and that the upper age limit should be 50 years and that the combination of ATG and ciclosporin remains the gold standard for IST. Scheinberg provided an overview and update of various treatment options for SAA including IST and transplantation.

Strengths and limitations
One of the strengths of this review is the broadness of the search strategy such that study retrieval bias is very unlikely. We restricted the inclusion of studies to RCTs and prospective non-RCTs that were compatible with ‘Mendelian randomisation’ to avoid excess risk of bias. We assumed a possible ‘Mendelian randomisation’ in the three included studies, though, the authors did not...

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**Table 2** Risk of bias of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Blinding of assessment of overall mortality</th>
<th>Incomplete outcome data</th>
<th>Selective reporting</th>
<th>Other bias</th>
<th>Comparable baseline characteristics</th>
<th>Concurrent control</th>
<th>Overall judgement of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayever et al.</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High*</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Führer et al.</td>
<td>Low</td>
<td>High</td>
<td>High†</td>
<td>High†</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Gratwohl et al.</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

*Bayever et al.: the authors reported the study results at an early time point before all planned data had been gathered: ‘We present this interim report (…).’
†Führer et al.: In the 2005 update, overall survival, secondary clonal disease or malignancies, and also relapse were not reported separately for the two distinct treatment groups. Rather, the results were presented for two subgroups according to disease severity. This was different from the earlier report of the same study published in 1998 covering the study period from 1993 to 1997. See figure 1 and table 1 of the article.
‡Führer et al.: financial support was provided by two pharmaceutical companies.

**Figure 2** Mortality in the donor group (MSD-HSCT) versus the no donor group (IST); effect: HR; random-effects model. SE calculated from data presented in the Kaplan-Meier graph of the article (MSD-HSCT, first-line allogeneic haematopoietic stem cell transplantation of bone marrow of HLA-matched sibling donors; log, logarithm; IST, first-line immunosuppressive therapy; IV, inverse variance).
mention this approach and did not report what proportion of patients with an MSD actually received the transplant. Thus, crucial information is lacking to judge the compliance of patients and the significance of the assumed concept of natural allocation. Nevertheless, the included data are too scarce and too biased to allow any conclusion on the comparative effectiveness of MSD-HSCT and IST. The rates of adverse events, such as treatment-related mortality, graft failure, no response to IST and GVHD, are unusually high, which may be explained by the age of the studies (starting in 1976). We did not separate horse ATG from rabbit ATG, although the type of animal as the origin of ATG was explained by the age of the studies (starting in 1976). All data were collected about 15 up to more than 30 years ago. Thus, the results may not be applicable to current modern standard care. Use of ‘Mendelian randomisation’ is no guarantee that bias is minimised. This may be because tissue typing data may not be accurate. Patients may have only one sibling either in the donor or in the no donor group. Large families have a greater chance of finding a donor. Therefore, designing a non-RCT by applying ‘Mendelian randomisation’ requires careful thought to effectively reduce bias and control for potential confounders. There is a time lag in patients with siblings because tissue typing and readiness for assignment to treatment group may possibly take several months. 

Nitsch et al. described the limits to causal inference based on ‘Mendelian randomisation’.

### CONCLUSIONS

There are insufficient and biased data that do not allow any firm conclusions to be made about the comparative effectiveness of MSD-HSCT and IST. Patients should be made aware of the early treatment-related mortality and the burden of GVHD after HSCT. Patients treated with IST should also be made aware that the disease may recur after initial successful treatment, and that life-threatening late clonal and malignant disease after IST may occur in a higher percentage compared with HSCT.

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#### Contributors

FP involved in the design, search strategy, study selection, data extraction, data analysis and writing the manuscript. AL involved in the methodological perspective, reviewing the manuscript.

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#### Competing interests

None.

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#### Data sharing statement

No additional data are available.

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Stem cell transplantation of matched sibling donors compared with immunosuppressive therapy for acquired severe aplastic anaemia: a Cochrane systematic review

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