9.1.2 Drugs used in hypoplastic, haemolytic and renal anaemias

8.2 Drugs affecting the immune response

(เฉพาะ Antithymocyte globulin, rabbit: rabbit ATG)

No.	ชื่อยา	รูปแบบยา	เหตุผล/เงื่อนไข
1	Ciclosporin (cyclosporine)	Cap, oral sol, oral susp, sterile sol	บัญชี ค *เงื่อนไข* กรณีผู้ป่วยไตมีเงื่อนไข คือ 1. กรณีผู้ป่วยปลูกถ่ายไตในระยะ maintenance therapy ให้ใช้ยารับประทานชนิด microemulsion 2. ใช้กับผู้ป่วย mininal change disease (MCD) ที่มี relapse บ่อย 3. ใช้กับผู้ป่วย focal segmental glomerulosclerosis (FSGS) ที่ดื้อต่อ prednisolone และ cyclophosphamide
2	Methylprednisolone	Sterile pwdr/sterile susp (as hemisuccinate or sodium succinate or acetate)	บัญชี ค *เงื่อนไข* 1. ใช้สำหรับ induction therapy ในการปลูกถ่ายอวัยวะ 2. ใช้สำหรับ acute rejection ในการปลูกถ่ายอวัยวะ (renal allograft acute rejection), SLE ชนิดรุนแรง, glomerulonephritis ชนิดรุนแรง, vasculitis, aplastic anemia, idiopathic thrombocytpenic purpura, demyelinating disease
3	Antithymocyte globulin, rabbit (ATG)	Sterile pwdr/sterile sol	บัญชี จ(2) *เงื่อนไข* 1. ใช้เป็น first-line drug ในการรักษาภาวะ renal allograft acute rejection ที่มีพยาธิสภาพรุนแรง 2. ใช้กับผู้ป่วยที่ไม่ตอบสนองต่อ pulse methylprednisolone 3. ใช้ในการรักษา severe aplastic anemia

1. ข้อมูลโดยสรุป

ความจำเป็นด้านสุขภาพ: Aplastic anemia เป็นโรคที่ไขกระดูกไม่สามารถสร้างเม็ดเลือดได้ กรณีที่เป็นรุนแรงมักเสียชีวิตด้วยเลือดออกหรือการติดเชื้อ และในอดีตแม้ว่าผู้ป่วยที่เป็นรุนแรงจะประสบความสำเร็จในการรักษา แต่มากกว่าร้อยละ 70 ก็เสียชีวิตภายใน 1 ปี[1, 2]

จำนวนผู้ป่วย: อุบัติการณ์ 192 – 319 รายต่อปี (3.0 – 5.0 ต่อประชากรล้านคนต่อปี ไม่พบข้อมูลจำแนกผู้ป่วยตามความรุนแรงของโรค)[3, 4]

ประสิทธิภาพ: ATG เป็นมาตรฐานการรักษา severe aplastic anemia ในผู้ป่วยที่ไม่สามารถปลูกถ่ายไขกระดูกได้ [2, 5, 6] โดยสูตรการรักษาที่มีประสิทธิภาพในการลดอัตราการเสียชีวิตได้สูงสุดคือ horse ATG + cyclosporine[7-9] (3-year overall survival horse ATG *vs* rabbit ATG: 96% *vs* 76%; P = .04)[9]

ความปลอดภัย: อาการไม่พึงประสงค์ที่สำคัญ ได้แก่ serum sickness, febrile neutropenia และการติดเชื้อ[9]

ค่าใช้จ่าย: ราคายาและค่าใช้จ่ายเฉพาะยา ATG ตามตารางที่ 2

ตารางที่ 1 ราคา ปริมาณการผลิต/นำเข้าปี 2554 และค่าใช้จ่ายของยา antithymocyte globulin, rabbit

ชื่อยา	**รูปแบบยา**	**มูลค่าการนำเข้าปี 2553 (บาท)**	**ราคายาเฉลี่ย (บาท)**	**ราคายาต่อคอร์สการรักษา**
Antithymocyte globulin (Thymoglobuline®)	Sterile powder 25 mg/vial (5 mL)	3,181,877	9,200.00 (เม.ย.–มิ.ย. 2554)	5-day course = **331**,200.00 ฿ (3.0mg/kg/day * 60kg * 5days * 9,200฿/vial) / 25 mg/vial)
Antithymocyte globulin (ATG-Fresenius®)	Sterile powder 100 mg/vial (5 mL)	20,240,000	9,200.00 (ก.ค.-ก.ย. 2553)	5-7day course = **198**,720.00 ฿ (6.0mg/kg/day * 60kg * 6days * 9,200฿/vial) / 100mg/vial)
Budget impact bye incidence rate			Budget impact bye incidence + relapse rate 35.2%[10]	
Incidence rate[3, 4]	Thymoglobuline®	ATG-Fresenius®	Thymoglobuline®	ATG-Fresenius®
3.0 / 10^6	**63**,469,446.09	**38**,081,667.65	**85**,810,691.12	**51**,486,414.67
5.0 / 10^6	**105**,782,410.15	**63**,469,446.09	**143**,017,818.53	**85**,810,691.12

หมายเหตุ: - ไม่มีบริษัทยายื่นเสนอราคา ATG ไว้ในบัญชียาหลักแห่งชาติ

- ไม่พบข้อมูลทางระบาดวิทยาที่จำแนกกลุ่มผู้ป่วยตามระดับความรุนแรงของโรค

คณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติ พิจารณาแล้วเห็นชอบให้ย้ายเป็นบัญชี จ(2)

2. แนวทางการจัดทำข้อมูล

การพิจารณายา จ๒ มีเกณฑ์การพิจารณานอกเหนือจากยาทั่วไป คือ “เป็นยาที่จำเป็นต้องใช้สำหรับผู้ป่วยเฉพาะราย มีจำนวนผู้ป่วยไม่มากและยามีค่าใช้จ่ายสูงที่ส่งผลกระทบต่อความสามารถในการจ่ายของรัฐ ซึ่งค่าใช้จ่ายที่เกิดขึ้น รัฐสามารถรับภาระค่าใช้จ่ายได้ โดยจัดระบบบริหารจัดการยาที่เหมาะสม”

ฝ่ายเลขานุการฯ จึงได้จัดทำข้อมูลที่เกี่ยวข้องกับประเด็นดังกล่าว โดยสืบค้นจากฐานข้อมูลต่างประเทศ เช่น องค์การอนามัยโลก, PBS Australia, British National Formulary, Lothian Joint Formulary, Micromedex, Uptodate, NICE guidance, NSH evidence, Pubmed และ BMJ clinical evidence

3. **รายละเอียดข้อมูลเชิงวิชาการ**

3.1 ข้อบ่งใช้ของยา antithymocyte globulin, rabbit ที่ขึ้นทะเบียนในประเทศไทย[11]

ATG-Fresenius® (1C 7/36)

ATG- Fresenius เป็นยาชีววัตถุ ที่ใช้ป้องกันและรักษาการตอบสนองทางภูมิคุ้มกันของร่างกายต่อกระบวนการเปลี่ยนเนื้อเยื่อและอวัยวะและใช้สำหรับ

1. รักษาโรคโลหิตจางอะพลาสติกชนิดรุนแรง

ATG- Fresenius มีข้อบ่งใช้ร่วมกับยากดภูมิคุ้มกันอื่น ๆ (เช่น เมธิลเพรดนิโซโลน หรือยายับยั้งแคลซินูริน) เพื่อรักษาโรคโลหิตจางอะพลาสติกชนิดรุนแรง

2. รักษาโรค graft-versus-host (GvHD)

ใช้ในผู้ป่วยปลูกถ่ายอวัยวะ

3. ป้องกันโรค graft-versus-host (GvHD)

ใช้ในผู้ป่วยก่อนการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิต (Hematopoietic Stem Cell Transplantaion, HSCT)

ATG-Fresenius สามารถใช้ในผู้ป่วยก่อนการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิตเพื่อลดโอกาสการเกิดโรค graft-versus-host ทั้งชนิดเฉียบพลันและเรื้อรัง ซึ่งสามารถใช้ในกรณีการปลูกถ่ายเซลล์ต้นกำเนิดจากผู้บริจาคที่เป็นญาติและไม่ใช่ญาติ รักษาโรคทางโลหิตวิทยาทั้งชนิด malignant และ non-malignant บางชนิด (malignant or non-malignant hematopoietic disorders)

ATG-Fresenius สามารถใช้ร่วมกับ cyclosporin A และ methotrexate เพื่อป้องกัน GvHD ในการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิตจากผู้บริจาคที่ไม่ใช่ญาติ

4. ใช้ป้องกันและรักษาการตอบสนองทางภูมิคุ้มกันของร่างกายต่อกระบวนการเปลี่ยนเนื้อเยื่อและอวัยวะ

ขนาดที่ใช้: Treatment of severe aplastic anemia 0.25-0.375 mL **(5-7.5 mg)/kg body wt/day** over 5-7 days. [MIMS online ตรวจสอบแล้วไม่ตรงกับเอกสารกำกับยาที่ขึ้นทะเบียนไว้ 3-5 mg/kg/day]

Thymoglobuline® (1C 36/52)

การปลูกถ่ายอวัยวะ

- ใช้ป้องกันหรือรักษาปฏิกิริยาการไม่ยอมรับเนื้อเยื่อที่ปลูกถ่าย โดยเฉพาะการปลูกเนื้อเยื่อของไต หัวใจ ตับอ่อน หรือตับ

โลหิตวิทยา

- รักษาโรคโลหิตจางชนิดอพลาสติก (aplastic anaemia)
- รักษาปฏิกิริยาการเกิด Graft-Versus-Host Disease อย่างเฉียบพลัน

ขนาดที่ใช้: Aplastic anemia **2.5-3.5 mg/kg/day** for 5 consecutive days, corresponding to cumulative dose of 12.5-17.5 mg/kg. [MIMS online ตรวจสอบแล้วตรงกับเอกสารกำกับยาในทะเบียน]

3.2 ข้อมูลจากรายการยาในต่างประเทศ

3.2.1 ข้อมูลจาก WHO Model Formulary 2008[12]

ไม่พบข้อมูล

3.2.2 ข้อมูลจาก WHO Model Lists 2011 (unedited version)[13]

ไม่พบข้อมูล

3.2.3 ข้อมูลจาก Australian Pharmaceutical Benefit Scheme 2011, Oct[14]

ไม่พบข้อมูล

3.2.4 ข้อมูลจาก Lothian Joint Formulary 2011[15]

ไม่พบข้อมูล

3.2.5 ข้อมูลจาก British National Formulary 62[16]

จากการสืบค้นด้วยคำสำคัญ “aplastic anemia” เมื่อวันที่ 20 มกราคม 2555 ไม่พบข้อมูล

จากการสืบค้นด้วยคำสำคัญ “antithymocyte” เมื่อวันที่ 20 มกราคม 2555 ไม่ได้กล่าวถึงการใช้ใน aplastic anemia

3.3 ข้อมูลจาก drug monographs

3.3.1 ข้อมูลจาก MicroMedex 2011

Micromedex ประเมินเฉพาะ horse ATG แต่ไม่ได้ทำการประเมิน rabbit ATG

ตารางที่ 2 การประเมินยากลุ่ม anticoagulants ชนิดฉีด โดย MicroMedex 2011[17]

Indications	Evaluation	Methylprednisolone	Antithymocyte globulin (equine)	Antithymocyte globulin (rabbit)	Cyclosporine
Aplastic anemia	US FDA Approval	No	Yes	-	No
	Efficacy	I	E	-	F
	Recommendation	IIb	IIa	-	IIa
	Strength of evidence	B	B	-	B

หมายเหตุ: ตัวย่อ US FDA approval = การอนุมัติข้อบ่งใช้โดยองค์การอาหารและยาสหรัฐอเมริกา, yr = years, mo = months; *MicroMedex efficacy* ตัวย่อ E = effective, F = evidence favors efficacy, I = evidence is inconclusive, X = ineffective; *MicroMedex recommendations class* แบ่งเป็น I, IIa, IIb, III, และ indeterminant ซึ่ง I = การใช้ยาเป็นประโยชน์และควรให้ผู้ป่วยใช้, IIa = ผู้ป่วยส่วนมากได้รับประโยชน์จากการใช้ยา, IIb = ผู้ป่วยอาจได้รับประโยชน์จากการใช้ยา จึงแนะนำให้พิจารณาในบางกรณี, III = การใช้ยาไม่มีประโยชน์ ควรหลีกเลี่ยง, indeterminant = ไม่สามารถสรุปได้จากหลักฐานที่มี; *MicroMedex strength of evidence* แบ่งเป็น category A, B, C, no evidence ซึ่ง A = มีหลักฐานที่เป็น meta-analysis จาก randomized-controlled trial (RCT) ซึ่งเป็นไปในทางเดียวกัน หรือ RCT ที่ดี หรือที่มีผู้เข้าร่วมการทดลองจำนวนมาก, B = มีหลักฐานที่เป็น meta-analysis จาก RCT ซึ่งขัดแย้งกัน มี RCT ที่มีผู้เข้าร่วมการทดลองน้อย ออกแบบการทดลองไม่ดี หรือไม่ใช่การทดลองแบบ RCT, C = เป็น expert’s opinion, case reports, หรือ case series

Methylprednisolone

- b) Summary:

- Methylprednisolone alone or in combination with antithymocyte globulin was effective in some but not other patients with aplastic anemia (Motoji et al, 1990; Pulver & Flaum, 1987; Issaragrisil & Painkijagum, 1985)

Cyclosporine

- b) Summary:

- The combination of horse antithymocyte globulin ATG) and cyclosporine was more effective than cyclosporine alone for the treatment of non-severe aplastic anemia.

Antithymocyte globulin (equine)

- b) Summary:

- Indicated for the treatment of moderate to severe aplastic anemia in patients who are unsuitable for bone marrow transplantation (Prod Info ATGAM(R) IV injection, 2005)
- One trial was terminated early due to excess morbidity and mortality in the high-dose cyclophosphamide arm (Tisdale et al, 2000)

3.3.2 ข้อมูลจาก Martindale 2011[17]

ในการรักษา aplastic anaemia ยังแบ่งตามช่วงอายุ โดยผู้ป่วยที่อายุน้อยกว่า 40 ปี ควรได้รับการพิจารณารักษาด้วยการปลูกถ่ายไขกระดูกซึ่งช่วยให้หายขาดได้ในระยะยาว แต่ถ้าไม่สามารถหาไขกระดูกที่เหมาะสมได้ อาจพิจารณาให้ยากดภูมิคุ้มกัน เช่น ATG ซึ่งผู้ป่วยมักตอบสนองร้อยละ 50 ทั้งนี้ หากให้ร่วมกับ ciclosporin จะช่วยให้การตอบสนองสูงขึ้นเป็นร้อยละ 60 - 80 และมีอัตราการรอดชีวิตที่ 5 ปี เป็นร้อยละ 75 – 90 สำหรับผู้ป่วยที่กลับมาเป็นซ้ำหรือไม่ตอบสนองต่อการรักษา ควรได้รับ ATG ซ้ำแต่ต้องไม่ต่ำกว่า 3 เดือนหลังจากการรักษาครั้งแรก

ผู้ป่วย aplastic anaemia ที่ไม่รุนแรง ควรได้รับการรักษาแบบประคับประคองเท่านั้น อย่างไรก็ตาม หากจำเป็นต้องพึ่งการให้เลือดหรือ neutrophil ต่ำจนเสี่ยงต่อการติดเชื้อ ก็อาจพิจารณาให้ยากดภูมิคุ้มกันได้

- **Aplastic anaemia**
  - Aplastic anaemia is characterised by pancytopenia (a deficiency of all cellular elements of the blood) and hypoplasia of the bone marrow, with less than 25% of the marrow occupied by haematopoietic cells but without evident fibrosis or malignant infiltration. It is relatively rare, although it may be somewhat more common in the Far East, and is mainly seen in younger adults. Some forms, such as Fanconi's anaemia, are inherited but most are induced, for example by the effects of cytotoxic drugs or radiation, idiosyncratic reactions to other drugs, seronegative fulminant hepatitis, or auto-immune reactions. Since all cell lines are affected patients develop thrombocytopenia and neutropenia as well as anaemia, and symptoms include bleeding syndromes and infections as well as typical symptoms of anaemia. Paroxysmal nocturnal haemoglobinuria (see Haemolytic Anaemia, Ref.), in which genetic mutation causes the production of abnormal blood cells and results in haemolysis, can be associated with aplastic anaemia.
  - Although spontaneous recovery has occurred, untreated aplastic anaemia is usually fatal. Management may be divided into supportive care and attempts to restore bone-marrow function with bone marrow transplantation or immunosuppression, and has been the subject of guidelines and reviews. (1-4)
  - Supportive care involves the prevention and treatment of infection (see Infections in Immunocompromised Patients, Ref.), the control of haemorrhage with platelet concentrates, and where necessary, infusions of red blood cells (with platelets to prevent haemorrhage) for anaemia. The risk of developing alloimmunisation, which can result in platelet refractoriness and increase the risk of graft rejection after allogeneic bone marrow transplantation, may be reduced by the use of leucocyte-depleted red cells and platelets. Some guidelines (4) also recommend the use of irradiated blood products in patients receiving antilymphocyte immunoglobulin, although evidence to support this is lacking and practice varies worldwide.
  - In patients aged under 40 years with severe disease and with a suitable HLA-identical sibling donor, bone marrow transplantation offers the prospect of long-term cure, and is considered the treatment of choice. (1,2,4,5) Ideally this should be performed early before the patient has received too many transfusions, which increase the risk of rejection, and before infection develops. Bone marrow stem cells are recommended because chronic graft-versus-host disease and overall survival may be worse when peripheral blood stem cells are used. (2,4) Umbilical cord blood is an alternative source of stem cells and may be associated with less acute and chronic graft-versus-host disease than bone marrow transplantation. (4) However, the use of cord blood is limited by the low number of cells that can be obtained.

- In patients unsuitable for bone marrow transplantation, or where a suitable sibling donor is not available, treatment with immunosuppressants may be tried. About 50% of patients are reported to respond to a course of antilymphocyte immunoglobulin, and the addition of ciclosporin further improves response rates to between 60 and 80% and 5-year survival to between 75 and 90%. (1,4) However, one long-term study (6) providing follow-up data for 11 years has found no significant difference in survival between regimens of antilymphocyte immunoglobulin with or without ciclosporin. (6) Response to treatment is usually delayed, and starts after about 3 to 4 months. (4) Ciclosporin has been used alone but is less effective than antilymphocyte immunoglobulin. (1,2)
- Despite these good rates of response with the addition of ciclosporin, relapse is not uncommon. (7) A second course of antilymphocyte immunoglobulin is recommended if there is no response, or there is relapse, after 3 months. (4) Ciclosporin is continued after a response has occurred and until the blood count has been stable for at least 12 months; it may then be slowly withdrawn, usually over many months and depending on blood counts. (4) Some patients may require continued therapy. (2,3)
- In patients with severe aplastic anaemia who have failed at least 1 course of antilymphocyte immunoglobulin and ciclosporin, and who are less than 50 years old, a matched unrelated bone marrow transplantation using a fludarabine-based regimen without irradiation may be considered. (4)
- Good response rates have been reported from combined regimens including a granulocyte colony-stimulating factor. (8) However, there are concerns about long-term use and the role of these factors is still under investigation. (2,4,9) There has been interest in the use of other haematopoietic growth factors including granulocyte-macrophage colony-stimulating factor, ancestim (stem cell factor), epoetin, interleukin-1, interleukin-3, and interleukin-6, either alone or with immunosuppression, but results have generally been poor or studies stopped because of toxicity, and so the use of these factors is not recommended. (4,9) However, short courses of granulocyte colony-stimulating factor may be considered for supportive therapy in neutropenic patients with severe systemic infections that are not responding to antibacterial or antifungal therapy. (4) Neutrophil responses are usually seen in patients with non-severe aplastic anaemia who have residual marrow granulocytopenic activity.
- Oxymetholone was used extensively before the availability of antilymphocyte immunoglobulin and ciclosporin. It can increase the response to antilymphocyte immunoglobulin alone, but it can be hepatotoxic and causes virilisation, and is generally used for patients who have failed several courses of antilymphocyte immunoglobulin with ciclosporin, or where this regimen cannot be used. (4) Cyclophosphamide is commonly used in preparation for bone marrow transplantation and complete remission has also been reported with high-dose cyclophosphamide alone. (10,11) However, a randomised study (12) of high-dose cyclophosphamide plus ciclosporin compared with conventional immunosuppression was stopped early when a higher mortality was seen in those receiving cyclophosphamide. Further follow-up (13) also found that relapse rates were no different. Nonetheless, cyclophosphamide continues to be of investigational interest. (3)
- Responses to immunosuppressants are often partial, but this may be sufficient to free the patient from dependency on transfusions and intensive antibacterial cover, and is considered well worth achieving. (1) Nevertheless, the procedure is not curative; patients appear to retain some underlying defect in marrow function, and in the long term about 15% of them develop leukaemias or myelodysplasias. (1)
- Children with severe aplastic anaemia are treated similarly to adults. (14,15) Although some reports have suggested that the response to immunosuppressant therapy may be lower in children under 5 years of age, others have shown the opposite. (14) The choice of treatment in children may also need to take into account the potential long-term adverse effects of treatment, particularly with immunosuppressants or irradiation, on endocrine function, growth, fertility, and the development of secondary malignancies.
- Older patients tend to be treated with immunosuppressant therapy rather than bone marrow transplantation. (4) A retrospective cohort study (16) that compared patients older than 50 years with younger patients found that more older patients had received ciclosporin alone, that the response to immunosuppression was independent of age at the time of treatment, and that although survival decreased with age deaths were similar to those in a general population and were not related to the type of treatment or the number of courses of treatment.
- The outcome of pregnancy in women who had previously been treated for aplastic anaemia with an immunosuppressant regimen has been described. (17) Of 36 pregnancies, 22 were uncomplicated and 7 were complicated by relapse of aplastic anaemia; complications appeared to be more likely in women with

low platelet counts and paroxysmal nocturnal haemoglobinuria. Rarely, aplastic anaemia can develop during pregnancy, and although the disease may remit spontaneously after termination or delivery, this does not occur in all cases. (18,19) Supportive care is the mainstay for management of aplastic anaemia during pregnancy, although the use of ciclosporin may be considered if transfusions are required. (4)

- Patients with non-severe aplastic anaemia may require supportive therapy only. However, those who are transfusion-dependent, (4,20) or who have significant neutropenia with an associated risk of infection, (4) may be candidates for immunosuppressive therapy. For children, bone marrow transplantation from an HLA-identical sibling may be considered in those with non-severe disease who are transfusion-dependent, particularly if the blood count is falling. (4)

3.4 ข้อมูลจาก practice guidelines และการทบทวนวรรณกรรม

3.4.1 ข้อมูลจาก uptodate online 19.3

ผู้เขียนบทความแนะนำว่า ผู้ป่วย severe หรือ very severe aplastic anaemia ที่อายุมากกว่า 45 ปี ควรรักษาด้วยยากดภูมิคุ้มกันมากกว่าการปลูกถ่ายไขกระดูก เพราะผู้ป่วยที่อายุมากกว่า 45 ปีมีความเสี่ยงสูงต่อการเกิด graft versus host disease

สำหรับยากดภูมิคุ้มกันที่แนะนำคือ ATG + ciclosporin และ corticosteroids สำหรับ ATG นั้นแนะนำ horse ATG มากกว่า rabbit ATG เนื่องจากการศึกษาเปรียบเทียบระหว่างยาทั้งสองพบว่า กลุ่มผู้ป่วยที่ได้รับ horse ATG มีอัตราการรอดชีวิต 3 ปี ร้อยละ 96 (95%CI 90 - 100) ในขณะที่ rabbit ATG เป็นร้อยละ 76 (95%CI 61 - 95)

Schrier 2011 (Patho)[1]

INTRODUCTION — Aplastic anemia is characterized by diminished or absent hematopoietic precursors in the bone marrow, most often due to injury to the pluripotent stem cell. The designation "aplastic anemia" is a misnomer because the disorder is defined as pancytopenia rather than anemia [1]. The disease is estimated to occur in two to four subjects per million population per year [1,2].

CAUSES AND MECHANISMS OF STEM CELL FAILURE — Aplastic anemia is a specific disease entity reflecting a deficiency of hematopoietic stem cells, resulting in peripheral pancytopenia and bone marrow aplasia (table 1). In contrast, bone marrow failure is a more encompassing term that describes pancytopenia from a variety of different mechanisms. Examples include bone marrow replacement by tumor or fibrosis, and myelodysplasia, in which the stem cells are malignant, may be present in increased numbers, but do not mature normally (table 2).

Schrier 2011 (Treatment)[2]

SUMMARY AND RECOMMENDATIONS

Prognosis — The prognosis of aplastic anemia (AA) depends upon two factors, disease severity and patient age.

- Disease severity — Depending on the degree of reduction of marrow cellularity and the amount and degree of cytopenia (eg, anemia, thrombocytopenia, neutropenia), AA is graded from moderate to severe (SAA) to very severe (vSAA). (See 'Disease severity' above.)
- Effect of age — There is a strong inverse relation between patient age and five-year survival in patients with AA. (See 'Patient age' above.)

Unless patients with SAA or vSAA are successfully treated, over 70 percent will be dead within one year. At any degree of severity of AA, the outcome is worse in older patients. For patients with moderate AA, treatment recommendations are unclear. With progressive cytopenias, particularly severe neutropenia and/or transfusion dependence, treatment with HCT or immunosuppression should be considered.

Treatment — Treatment of AA includes withdrawal of potentially offending agents (table 1), supportive care (eg, transfusion, antibiotics), and some form of definitive therapy (eg, hematopoietic cell transplantation, immunosuppressive regimens). Blood and platelet transfusions should be used selectively in patients who are candidates for HCT to avoid sensitization.

- Hematopoietic cell transplantation — Allogeneic hematopoietic cell transplantation (HCT) is curative in AA, but is limited by the availability of an HLA-matched sibling as well as by the potentially fatal consequences of graft

versus host disease in patients over the age of 40 to 45. (See "Hematopoietic cell transplantation in aplastic anemia" and 'Treatment overview' above.)

- Immunosuppressive regimens — Immunosuppressive regimens are not curative, but can be associated with long-term survival. (See 'Immunosuppressive regimens' above.)

Under age 20 — In patients with SAA or vSAA <20 years of age with an HLA-matched sibling, we recommend treatment with allogeneic HCT over treatment with an immunosuppressive regimen (Grade 1B). For those who do not have a matched sibling donor we suggest the use of immunosuppressive therapy over the use of matched unrelated, mismatched related, or mismatched unrelated HCT (Grade 2C). (See "Hematopoietic cell transplantation in aplastic anemia", section on 'Comparison with immunosuppression'.)

Age 20 to 45 years — In patients with SAA or vSAA 20 to 45 years of age in otherwise excellent health with a fully HLA-matched sibling donor, we recommend treatment with allogeneic HCT over treatment with an immunosuppressive regimen (Grade 1C). For those without a matched sibling donor, we suggest the use of immunosuppressive therapy over the use of matched unrelated, mismatched related, or mismatched unrelated HCT (Grade 2C).

Age over 45 — In patients with SAA or vSAA over the age of 45, we suggest the use of immunosuppressive therapy over HCT because of the very high risk of graft versus host disease in patients >45 (Grade 2B). (See 'Treatment overview' above.)

Immunosuppression — For immunosuppression in patients with moderate AA, SAA, or vSAA we recommend the combined use of anti-thymocyte globulin, cyclosporine, and corticosteroids, without granulocyte-colony stimulating factor, over the use of less intensive regimens (Grade 1B). (See 'ATG and cyclosporine' above.)

- We recommend the use of horse ATG over rabbit ATG for this purpose (Grade 1A). (See 'Horse versus rabbit ATG' above.)
- Patients relapsing after successful treatment can be re-treated with this regimen with excellent results and no survival disadvantage.

ส่วนขยายความ

PROGNOSIS

Disease severity — The clinical outcome in AA is dependent upon the severity of the pancytopenia and patient age.

Moderate AA — The criteria for moderate AA include:

- Marrow cellularity <30 percent
- Absence of severe pancytopenia
- Depression of at least two of three blood elements below normal

Severe AA (SAA) — The criteria for severe aplastic anemia (SAA) include [3]:

- A marrow biopsy showing <25 percent of normal cellularity, **or**
- A marrow showing <50 percent normal cellularity in which <30 percent of the cells are hematopoietic and at least two of the following are present: absolute reticulocyte count <40,000/microL; absolute neutrophil count (ANC) <500/microL (calculator 1); or platelet count <20,000/microL.

Very severe AA (vSAA) — The patient is considered to have very severe aplastic anemia (vSAA) if the criteria for SAA are met and the ANC is <200/microL (calculator 1).

Unless patients with SAA or vSAA are successfully treated, over 70 percent will be dead within one year [1]. In a retrospective review from the European Group for Blood and Marrow Transplantation (EBMT), the relative risk for a poor outcome following immunosuppressive treatment was 3.4 for patients with an ANC <200/microL (vSAA) and 1.5 in those with an ANC between 200 and 500/microL (SAA) compared with patients with higher ANCs [4].

Patient age — The prognosis of AA is influenced by patient age. The above report from the EBMT evaluated the effectiveness of immunosuppressive therapy in 810 patients with AA reported to the registry between 1974 and 1997 [4]. The response rate at 12 months was 62 percent. The response to therapy, relapse rate, and risk of clonal complications were similar in all three age groups studied (<49 years, 50 to 59 years, and >60 years). However, the five-year survival rate varied inversely and significantly with age, being 72, 57, and 50 percent, respectively, in the three groups. The increase in mortality in the older patients was mainly due to infection or bleeding. Most infections were acquired from endogenous microbial flora of the skin and gastrointestinal tract.

At any degree of severity of the AA in the EBMT review, the outcome was worse in older patients [4]. Among those with vSAA, the five-year survival rates for the three age groups mentioned above were 49, 40, and 21 percent, respectively; among those with moderate aplasia, the respective values were 86, 72, and 54 percent.

TREATMENT OVERVIEW — Treatment of AA should include withdrawal of potentially offending agents (table 1), supportive care (eg, transfusion, antibiotics), and some form of definitive therapy (eg, hematopoietic cell transplantation

(HCT), immunosuppressive regimens) for patients with severe or very severe AA [6,7]. Blood and platelet transfusions should be used selectively in patients who are candidates for HCT in order to avoid sensitization.

Under age 20 — For patients under age 20, allogeneic HCT should be performed promptly if a fully HLA-matched sibling donor is available. (See"Hematopoietic cell transplantation in aplastic anemia".)

Ages 20 to 45 — The approach to these patients is changing, because current transplantation programs appear to be capable of reducing the incidence and severity of GVHD. Preliminary studies suggest an improved outcome with cyclophosphamide/antithymocyte globulin conditioning prior to HCT to prevent rejection and cyclosporine plus methotrexate to reduce the incidence of acute or chronic GvHD [11]. Therefore, if a patient in this age group is in otherwise excellent health and has a fully HLA-matched sibling donor, allogeneic HCT could be the first choice [1,8]. (See "Hematopoietic cell transplantation in aplastic anemia".)

Over age 45 — GVHD is thought to be a very difficult problem for patients with AA over the age of 45 who receive hematopoietic cell transplantation; for these patients immunosuppressive therapy (IST) is recommended [8,9].

IMMUNOSUPPRESSIVE REGIMENS

ATG alone — Initial regimens often consisted of antithymocyte globulin (ATG) alone. According to one report, the response is dependent upon disease severity, with six-year survival rates of 71, 48, and 38 percent for patients with moderate AA, SAA, and vSAA, respectively [13]. Similar results were noted in the EBMT review with five-year survival rates of 79, 69, and 45 percent in these three groups [4]. The somewhat better outcomes in this report may result from the inclusion of some patients under the age of 45. Within each of these groups of severity, the outcome was inversely related to age (see'Patient age' above).

Another report compared lower and higher doses of methylprednisolone in 68 patients (not all of whom were over age 45) who were also treated with ATG and the androgen oxymetholone [10]. The actuarial four-year survival was similar in both groups (47 versus 43 percent); most of these patients had SAA.

ATG and cyclosporine — A more intensive regimen including ATG and cyclosporine appears to provide superior results compared with treatment with ATG alone in patients with SAA [1,19-21]. In our practice, we prefer the shorter, higher dose regimen, primarily because it reduces the length of hospitalization needed to infuse the ATG preparations. These are reviewed below.

A German trial randomly assigned patients with AA to receive ATG and methylprednisolone with or without cyclosporin A [21]. Patients receiving the three-drug regimen responded more rapidly, often following a single course of treatment, and had a higher response rate after four months than those treated with ATG and steroids alone (70 versus 41 percent). Although failure-free survival favored the group receiving cyclosporine, relapse rates at 11 years were similar in the two treatment arms (38 percent), as was overall survival.

In another study of 122 patients with SAA, 31 of whom were ≤18 years of age, the following regimen was used [19,22]:

- Horse ATG at a dose 40 mg/kg per day in 500 mL of saline given over four to six hours for four consecutive days.
- Prednisone or methylprednisolone in divided doses of 1 mg/kg per day. Steroids were given for two weeks, with the dose tapered so that the corticosteroids were discontinued by day 30.
- Cyclosporine, 10 to 12 mg/kg per day, given in two equally divided doses, aiming for trough levels of 100 to 200 ng/mL of serum or 500 to 800 ng/mL in whole blood. Cyclosporine is generally continued for about six months, although the dose may be tapered after one month to trough whole blood levels of 200 to 500 ng/mL.

Using this approach, improvement in blood counts occurred in 60 percent of patients after three months. The actuarial risk of relapse was 35 percent at five years. Most of the relapsing patients responded to additional courses of immunosuppression, and relapse was not associated with a significant survival disadvantage.

Evolution to a new hematologic diagnosis, most commonly monosomy 7, occurred in 13 patients. Sixty percent of evolving patients were dead within three years of the event; all had monosomy 7. Actuarial overall survival for the entire group was 55 percent at seven years, and was higher for responders at three months (86 versus 40 percent) as well as those <50 years of age (66 versus 38 percent).

Combination therapy may also be beneficial in patients with nonsevere AA [21]. This approach was evaluated in a prospective trial in which 115 such patients were randomly assigned to receive cyclosporine (CSA), alone or in combination with horse ATG [23]. Combination therapy was associated with a significantly higher overall response (74 percent, 57 percent complete responses) than CSA alone (46 percent, 23 percent complete) and a lower rate of disease progression requiring further therapy in six months (6 versus 25 percent). At 180 days, the prevalence of patients surviving free of transfusions was 67 percent in the CSA group and 90 percent in the ATG plus CSA group.

Horse versus rabbit ATG — A single center randomized trial compared horse ATG (ATGAM, 40 mg/kg per day for four days) with rabbit ATG (Thymoglobulin, 3.5 mg/kg per day for five days) in 120 consecutive patients with severe aplastic anemia, who were also treated with cyclosporine (10 mg/kg per day given in divided doses every day from day 1 and

continued for at least six months; dose adjusted to maintain trough blood levels of 200 to 400 ng/mL). The primary study endpoint was hematologic response at six months. Results, which showed clear superiority of the horse ATG preparation, included the following [36]:

- Hematologic response at six months was 68 (95% CI: 56 to 80) versus 37 (95% CI: 24 to 49) percent for those treated with horse versus rabbit ATG, respectively.
- Overall survival, when censored at the time of stem cell transplantation, also strongly favored use of horse ATG, with three-year overall survivals of 96 (95% CI: 90 to 100) versus 76 (95% CI: 61 to 95) percent, respectively.

At a median follow-up of 28 months, there were no significant differences between the two regimens in terms of the cumulative incidences of relapse or clonal evolution.

RELAPSING OR RESISTANT DISEASE

Retreatment with ATG — The therapeutic response to immunosuppressive therapy in AA is not a "cure," as is allogeneic HCT, and the responses are incomplete. Many of these patients continue to have marginal cytopenias, and 9 to 35 percent relapse with AA [13,20,48,49]. A review of 719 patients treated with immunosuppressive therapy noted an actuarial relapse rate of 35 percent at 14 years [49]. Relapse was not predicted by age or severity of disease.

- Approximately 50 to 65 percent of patients who relapse following a first successful course of ATG (with or without cyclosporine) respond to additional courses of immunosuppression (either repeated horse ATG or rabbit ATG) [20,50]. Although serum sickness occurs earlier with repeated courses of horse ATG, such regimens are generally well tolerated.
- The response rate to additional courses of immunosuppression for those who failed to respond to a first course of horse ATG has varied widely, from 10 to 77 percent in various studies [51-54], and was 30 percent in 22 patients who failed treatment with horse ATG and were subsequently treated with rabbit ATG [50].

In an uncontrolled trial, 30 patients with SAA who failed to respond to a schedule of horse ATG, cyclosporine, and G-CSF were treated with the following regimen [53]:

- Rabbit ATG (3.5 mg/kg, diluted in isotonic saline, IV over 6 to 8 hours, days 1 through 5)
- Methylprednisolone 2 mg/kg IV days 1 through 5 and 1 mg/kg IV on days 6 through 10, tapered within 30 days
- Cyclosporine 5 mg/kg PO days 1 to 180, slowly tapered thereafter
- G-CSF 5 microg/kg SQ days 1 to 90 (24 patients)

Transfusion independence was achieved in 23 of the 30 patients (77 percent) after a median time of 95 days, and 9 patients achieved complete remission. Overall survival rate was 93 percent at a median follow-up of 2.5 years, with no relapses to date. No anaphylaxis or major symptoms of allergic reaction were noted; female gender was the only factor predicting failure.

In the above review of 719 patients [49], those who responded to a second course of immunosuppressive therapy had an actuarial survival of 80 percent; this value was similar to that in patients who did not relapse (86 percent) and significantly better than that in patients not achieving a second response (49 percent). Other studies have confirmed the lack of survival disadvantage in relapsers who responded to a second course of immunosuppressive therapy [19,52].

Resistant disease — Unless patients with SAA or vSAA are successfully treated, over 70 percent will be dead within one year. For patients who do not respond to a repeat course of immunosuppressive therapy with ATG and cyclosporine and are not candidates for HCT, options include alemtuzumab and high-dose cyclophosphamide [56]. Enrollment in a well-conducted experimental protocol is strongly encouraged [12]. The ex vivo and in vivo use of recombinant transcription factors that govern stem and progenitor cell fate decisions in patients with marrow failure syndromes is being explored [57].

3.4.2 ข้อมูลจาก NICE guidance

จากการสืบค้นด้วยคำสำคัญ “aplastic anemia” หรือ “antithymocyte” เมื่อวันที่ 20 มกราคม ไม่พบผลลัพธ์ที่เกี่ยวข้อง

3.4.3 ข้อมูลจาก NHS evidence

จากการสืบค้นด้วยคำสำคัญ “aplastic anemia” พบจำนวนผลลัพธ์ ดังนี้

All results = 1,159

Practice guidelines = 85 → related = 1 (ซ้ำกับ Pubmed Marsh, et al., 2009)

แนวเวชปฏิบัติในการรักษา aplastic anaemia แนะนำการรักษาด้วยการปลูกถ่ายไขกระดูกในผู้ป่วย severe หรือ very severe aplastic anaemia ที่อายุน้อยกว่า 40 ส่วนการรักษาด้วยยากดภูมิคุ้มกันนั้น แนะนำในผู้ป่วย (1) non-severe aplastic anaemia ที่ต้องพึ่งการให้เลือด (2) ผู้ป่วย severe หรือ very severe aplastic anaemia ที่อายุ > 40 ปี (3) ผู้ป่วยที่อายุไม่เกิน 40 ปีซึ่งไม่สามารถหาไขกระดูกที่เหมาะสมได้

สำหรับยากดภูมิคุ้มกันที่เป็นตัวเลือก ได้แก่ ATG และ ciclosporin ซึ่งให้ผลการตอบสนองที่ร้อยละ 60 – 80 และมีอัตรการรอดชีวิต 5 ปีที่ร้อยละ 75 – 85 การรักษาด้วย ATG มักเห็นผลในเดือนที่ 3 – 4 ของการรักษา ดังนั้น ช่วงที่ยังไม่ตอบสนอง จำเป็นต้องรักษาด้วยการประคับประคองไปก่อน และผู้ป่วยร้อยละ 30 อาจกลับเป็นซ้ำ

Marsh, et al., 2009[5] และฉบับล่าสุดปี 2010

Summary of key recommendations

• Aplastic anaemia (AA) is a rare but heterogeneous disorder. The majority (70–80%) of these cases are categorised as idiopathic because their primary aetiology is unknown. In a subset of cases, a drug or infection can be identified that precipitates the bone marrow failure/ aplastic anaemia, although it is not clear why only some individuals are susceptible. In approximately 15–20% of patients the disease is constitutional/inherited, where the disease is familial and/or presents with one or more other somatic abnormalities.

• Definitive treatment

(1) Infection or uncontrolled bleeding should be treated first before giving immunosuppressive therapy. This also applies to patients scheduled for BMT, although it may sometimes be necessary to proceed straight to BMT in the presence of severe infection as a BMT may offer the best chance of early neutrophil recovery.

(2) Haemopoietic growth factors such as rHuEpo or G-CSF should not be used on their own in newly diagnosed patients in an attempt to 'treat' the aplastic anaemia.

(3) Prednisolone should not be used to treat patients with aplastic anaemia because it is ineffective and encourages bacterial and fungal infection.

(4) Allogeneic BMT from a human leucocyte antigen (HLA)-identical sibling donor is the initial treatment of choice for newly diagnosed patients if they have severe or very severe aplastic anaemia, are <40 years old and have an HLA-compatible sibling donor. There is no indication for using irradiation-based conditioning regimens for patients undergoing HLA-identical sibling BMT for aplastic anaemia. The recommended source of stem cells for transplantation in aplastic anaemia is bone marrow.

(5) Immunosuppressive therapy is recommended for (i) patients with non-severe aplastic anaemia who are transfusion dependent (ii) patients with severe or very severe disease who are >40 years old and (iii) younger patients with severe or very severe disease who do not have an HLA-identical sibling donor. The standard immunosuppressive regimen is a combination of antithymocyte globulin (ATG) and ciclosporin. ATG must only be given as an in-patient. Ciclosporin should be continued for at least 12 months after achieving maximal haematological response, followed by a very slow tapering, to reduce the risk of relapse. The routine use of long term G-CSF, or other haemopoietic growth factors, after ATG and ciclosporin, is not recommended outside the setting of prospective clinical trials.

(6) Matched unrelated donor (MUD) BMT may be considered when a patient has severe aplastic anaemia, has no matched sibling donor but a matched unrelated donor, is <50 years old (or 50–60 years old with good performance status), and has failed at least one course of ATG and ciclosporin. The optimal conditioning regimen for MUD BMT is uncertain, but currently a fludarabine, non-irradiation-based regimen is favoured for younger patients.

• There is a high risk (around 33%) of relapse of aplastic anaemia in pregnancy. Supportive care is the mainstay of treatment in pregnancy and the platelet count should be maintained >20 ท 109/l, if possible. It is safe to use ciclosporin in pregnancy.

Table IV. Definition of severity of aplastic anaemia.

Severe AA (Camitta *et al*, 1975)	BM cellularity <25%, or 25–50% with <30% residual haemopoietic cells* 2/3 of the following: Neutrophil count $<0{\cdot}5 \times 10^9$/l Platelet count $<20 \times 10^9$/l Reticulocyte count $<20 \times 10^9$/l
Very severe AA (Bacigalupo *et al*, 1988)	As for severe AA but neutrophils $<0{\cdot}2 \times 10^9$/l
Non-severe AA	Patients not fulfilling the criteria for severe or very severe aplastic anaemia

*Cellularity should be determined by comparison with normal controls (Tuzuner & Bennett, 1994).

6. Immunosuppressive therapy: antithymocyte globulin (ATG) and ciclosporin

6.1. Results of treatment

Immunosuppressive therapy using the combination of ATG and ciclosporin is associated with response rates of between 60% and 80% with current 5 year survival rates of around 75–85% (Bacigalupo et al, 2000a; Bacigalupo et al, 2000b, Fuhrer et al, 2005; Locasciulli et al, 2007). A recent study has shown that on multivariate analysis of response at 6 months, only younger age, absolute reticulocyte count (ARC) and absolute lymphocyte count (ALC), correlate with response to ATG. The lack of association with the absolute neutrophil response reflected a high number of early deaths in patients with very severe neutropenia. For patients with both ARC $\geq$ 25 x 10^9/l and ALC $\geq$ 1 x 10^9/l, the response was 83% compared with 41% for those with lower counts (Scheinberg et al, 2009). For severe aplastic anaemia, the event-free survival and response rate to ATG alone is significantly less than with the combination of ATG and ciclosporin (Bacigalupo et al, 2000a; Frickhofen et al, 2003), and for patients with non-severe aplastic anaemia the response to the combination of ATG and ciclosporin is significantly greater than with ciclosporin alone (Marsh et al, 1999). Response to ATG and ciclosporin is delayed and response usually does not start much before 3–4 months. This means that patients need to continue with regular red cell and platelet transfusional support and will remain neutropenic during this time period. Relapse may occur after immunosuppressive therapy. This was previously reported to be around 30% (Schrezenmeier et al, 1993) but with longer use and slower tailing of ciclosporin the rate is closer to 10% (Bacigalupo et al, 2000b). Patients are at risk of later clonal disease, 8% for MDS/AML, 10% for haemolytic PNH and 11% for solid tumours at 11 years (Frickhofen et al, 2003).

6.2. Indications

Immunosuppressive therapy is indicated for patients who are not eligible for sibling donor BMT. This includes (i) patients with non-severe aplastic anaemia who are dependent on red cell and/or platelet transfusions (ii) patients with non-severe aplastic anaemia who, although not transfusion-dependent, may have significant neutropenia and be at risk of infection (iii) patients with severe or very severe aplastic anaemia who are >40 years of age and (iv) younger patients with severe or very severe disease who lack an HLA-compatible sibling donor (Grade B recommendation; level IIb evidence). Children with non-severe aplastic anaemia with an HLA-identical sibling donor and who are transfusion-dependent, and particularly if the blood count is falling, may be considered for BMT.

For those patients with non-severe aplastic anaemia who are not dependent on either red cell or platelet transfusions, and maintain safe blood counts, it is reasonable to observe the blood count and monitor the patient regularly without initially instigating immunosuppressive therapy. The decision whether and when to start treatment is usually determined by the pattern of the blood counts, the individual patient's life-style and choice, and older age (see Section 6.4).

6.3. Administration

Antithymocyte globulin is a powerful immunosuppressive drug and its use in severely neutropenic patients requires very careful monitoring, prophylaxis and treatment of fevers and infections, as well as adequate (and sometimes intensive) platelet transfusional support (grade A recommendation; level Ib evidence).

In the UK, most of Europe and many other countries, the standard preparation of ATG has until recently been horse ATG (Lymphoglobuline; Genzyme). The rabbit preparation (Thymoglobuline; Genzyme) was usually reserved for second or subsequent courses. From June 2007, supply of horse ATG (Lymphoglobuline) was withdrawn due to manufacturing difficulties maintaining quality control. Rabbit ATG (Thymoglobuline) is therefore now recommended as first line treatment. Response rates to rabbit ATG are anticipated to be similar to horse ATG, based on (i) response rates when rabbit ATG is used for a second course (Di Bona et al, 1999; Scheinberg et al, 2006a) and (ii) both preparations have the same immunogen (thymocytes), similar production method and they bind to similar epitopes. To date, there have been only two studies using rabbit ATG as first line treatment for aplastic anaemia. In a small single centre phase II study of 13 patients with aplastic anaemia and 12 with low risk MDS, among the patients with aplastic anaemia, there were five complete responses and seven partial responses (Garg et al, 2009). Preliminary results from a Spanish retrospective multicentre study of 72 patients, reported an overall response rate of 46% (Vallejo et al, 2009). For a second course of ATG, options include giving rabbit ATG again or using an alternative preparation of horse ATG, such as ATGAM (Pharmacia and Upjohn Company, Kalamazoo, MI, USA).

6.5. Definition of response

There has previously been no agreement regarding the measurement of response to immunosuppressive therapy, with the result that it has been difficult to compare response rates. New criteria for response have recently been accepted by an expert committee on aplastic anaemia, and these are summarized in Table Va, b (Camitta, 2000). Responses should be confirmed by two or more blood counts at least 4 weeks apart, and should ideally be measured in patients who are not receiving haemopoietic growth factors (Camitta, 2000).

Table V. Criteria for response to immunosuppressive therapy in aplastic anaemia.

a. Response criteria for severe aplastic anaemia	
None	Still severe
Partial	Transfusion independent
	No longer meeting criteria for severe disease
Complete	Haemoglobin normal for age
	Neutrophil count $>1{\cdot}5 \times 10^9$/l
	Platelet count $>150 \times 10^9$/l
b. Response criteria for non-severe aplastic anaemia	
None	Worse or not meeting criteria below
Partial	Transfusion independence (if previously dependent)
	or doubling or normalisation of at least one cell line
	or increase of baseline haemoglobin of >30 g/l (if initially <6)
	or increase of baseline neutrophils of $>0{\cdot}5 \times 10^9$/l (if initially <0·5)
	or increase of baseline platelets of $>20 \times 10^9$/l (if initially <20)
Complete	Same criteria as for severe disease

3.4.4 ข้อมูลจาก practice guidelines ซึ่งสืบค้นจาก Pubmed

จากการสืบค้นฐานข้อมูล Pubmed ด้วยคำสำคัญ

Practice guidelines

(("Antilymphocyte Serum"[Mesh] OR "Aplastic anemia, idiopathic" [Supplementary Concept]) AND ("Antilymphocyte Serum"[Mesh] AND "Rabbits"[Mesh])) AND "Practice Guideline" [Publication Type]

Results = 0

(("Antilymphocyte Serum"[Mesh] OR "Aplastic anemia, idiopathic" [Supplementary Concept]) AND ("Antilymphocyte Serum"[Mesh])) AND "Practice Guideline" [Publication Type]

Results = 1

Related = 1 แต่ไม่สามารถเข้าถึงเอกสารฉบับเต็มได้ อย่างไรก็ตาม ผู้เขียนกลุ่มเดียวกันได้ออก guidelines ฉบับใหม่ในปี 2009 (Marsh, et al., 2009)

Systematic reviews

(((("Antilymphocyte Serum"[Mesh] OR "Aplastic anemia, idiopathic" [Supplementary Concept]) AND ("Antilymphocyte Serum"[Mesh] AND "Rabbits"[Mesh])) AND “Systematic”[Sb]) NOT "Randomized Controlled Trial" [Publication Type]

Results = 2

Related = 0

((("Antilymphocyte Serum"[Mesh] OR "Aplastic anemia, idiopathic" [Supplementary Concept]) AND ("Antilymphocyte Serum"[Mesh])) AND “Systematic”[Sb]) NOT "Randomized Controlled Trial" [Publication Type]

Results = 23

Related = 4 → abstract available = 2 → full article access = 0

Ann Pharmacother. 1996 Oct;30(10):1164-74.

Antithymocyte immunoglobulin in severe aplastic anemia and bone marrow transplantation.

Colby C, Stoukides CA, Spitzer TR.

Source

Massachusetts General Hospital, Boston 02114, USA.

Abstract

OBJECTIVE:

To review antithymocyte immunoglobulin (ATG) and its current role in the treatment of severe aplastic anemia (SAA), focusing on ATG in immunosuppressive therapy compared with bone marrow transplantation (BMT).

DATA SOURCES:

A MEDLINE search (1966 to 1996) of English-language literature and human subjects pertaining to ATG and BMT therapy in SAA was performed. Additional literature was obtained from reference lists of pertinent articles identified through the search.

STUDY SELECTION AND DATA EXTRACTION:

All articles were considered for possible inclusion in the review. Pertinent information, as judged by the authors, was selected for discussion.

DATA SYNTHESIS:

The hallmark of SAA is pancytopenia and bone marrow hypoplasia. Although the etiology in a majority of cases remains unknown, current data implicate an immune-mediated destruction of stem cells. ATG is a potent immunosuppressive agent and has emerged as an important therapy for patients with SAA. The exact mechanism of immunosuppressive action is not fully understood, although ATG appears to disrupt cell-mediated immune responses resulting in inhibition or altered T-cell function. Numerous trials have evaluated the use of ATG both as monotherapy and in combination with other immunosuppressive agents. Treatment with ATG in SAA has demonstrated a 40-70% response rate. Data suggest that intensive immunosuppressive therapy with ATG in combination with cyclosporine may provide the optimal immunosuppressive treatment. Questions still remain concerning complications and long-term survival of the patients. Although more than a 2-year follow-up shows a decline in mortality, a plateau in the survival curve was not achieved. BMT is a potential treatment for SAA. Although there is a high initial mortality due to treatment-related toxicities, successful marrow engraftment provides a cure for SAA. Many patients (75-90%) experience long-term survival after allogenic BMT. Age, donor availability, and severity of disease limit the number of eligible patients.

CONCLUSIONS:

Due to excellent results with BMT, it has become the therapy of choice for selected patients with SAA. For patients who are not eligible for BMT, intensive immunosuppressive therapy with ATG and cyclosporine is recommended. Further study to better understand the pathogenesis of SAA and prevent treatment-related complications is essential to provide the best care to all patients.

Acta Haematol. 2008;120(4):237-43. Epub 2009 Feb 25.

ATG plus cyclosporine reduces all-cause mortality in patients with severe aplastic anemia--systematic review and meta-analysis.

Gafter-Gvili A, Ram R, Gurion R, Paul M, Yeshurun M, Raanani P, Shpilberg O.

Source

Institute of Hematology, Davidoff Center, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel. anatga2@clalit.org.il

Abstract

BACKGROUND:

Immunosuppression is the therapeutic alternative for patients with aplastic anemia who are ineligible for allogeneic transplant. We aimed to assess the benefit of the combination of antithymocyte globulin (ATG) and cyclosporine (CsA).

METHODS:

We performed a systematic review and meta-analysis of all randomized controlled trials that compared ATG and CsA to ATG alone as first-line treatment for patients with severe and nonsevere aplastic anemia. The Cochrane Library, Medline, conference proceedings and references were searched until 2008. Relative risks (RR) with 95% confidence intervals (CIs) were estimated for each trial and pooled.

RESULTS:

Our search yielded 4 trials. For patients with severe aplastic anemia, there was a significant reduction in mortality in the ATG and CsA arm, which began at 3 months (RR = 0.50, 95% CI 0.29-0.85) and was maintained over a long follow-up of 5 years (RR = 0.58, 95 % CI 0.36-0.93). Conversely, in patients with nonsevere aplastic anemia, there was no difference in mortality.

CONCLUSIONS:

The combination of both drugs should be considered the gold standard only for patients with severe aplastic anemia.

Randomized controlled trials

(("Antilymphocyte Serum"[Mesh] OR "Aplastic anemia, idiopathic" [Supplementary Concept]) AND ("Antilymphocyte Serum"[Mesh] AND "Rabbits"[Mesh])) AND "Randomized Controlled Trial" [Publication Type]

Results = 42

Related = 1

(("Antilymphocyte Serum"[Mesh] OR "Aplastic anemia, idiopathic" [Supplementary Concept]) AND ("Antilymphocyte Serum"[Mesh])) AND "Randomized Controlled Trial" [Publication Type]

Results = 372

Related = 3 (เฉพาะการศึกษาที่ตีพิมพ์ตั้งแต่ปี 2000 ขึ้นไปจนปัจจุบัน และเป็นการศึกษาที่ทำให้ทราบถึงประสิทธิภาพของ antithymocyte globulin)

Frickhofen, et al., 2003[7]

Immunosuppression with antithymocyte globulin, (methyl)prednisolone, and cyclosporine A is considered the treatment of choice for the patient with aplastic anemia without a donor for standard-risk stem cell transpl antation. This consensus is

supported by the results of several series, including a randomized German trial. Here we report 11-year results of the latter trial. With stringent response criteria and 4 months as the time to evaluate responses, this analysis confirms the superiority of the cyclosporine regimen regarding the response rate in all patients treated (70% vs 41%, with or without cyclosporine; *P* _ .015) and in patients with severe aplastic anemia (65% vs 31%; *P* _ .011). Patients responded more rapidly after treatment with cyclosporine (median, 60 vs 82 days; *P* _ .019). Most patients treated with cyclosporine needed only one course of immunosuppression, whereas many patients treated without cyclosporine required repeated immunosuppressive treatment. Because of the efficacy of salvage treatment, overall survival was not different between the 2 treatment groups. However, failure-free survival favored the cyclosporine regimen (39% vs 24%; *P* _ .04). The relapse rate, projected at 38% after 11.3 years, was similar between the 2 treatment groups. Remissions were cyclosporine dependent in 26% of the patients responding to a regimen that included cyclosporine. Clonal or malignant diseases developed in 25% of the patients. These data demonstrate that antithymocyte globulin, methylprednisolone, and cyclosporin A are an effective regimen for the treatment of aplastic anemia. However, remissions are unstable, and secondary diseases are common. In contrast to the results of stem cell transplantation, most patients are not cured. (Blood. 2003;101: 1236-1242)

Osugi, et al., 2007[18]

We analyzed the outcomes of 44 children with hepatitis associated aplastic anemia (HAA) who received immunosuppressive therapy (IST) with antithymocyte globulin (ATG) and cyclosporine (CsA). Fourteen (31.8%) patients achieved complete response and 17 (38.6%) achieved partial response, for an overall response rate of 70.4% after 6 months. Seven non-responders received bone marrow transplantation from an HLAmatched unrelated donor and 6 out of 7 are alive. The probability of overall survival at 10 years was 88.3±4.9%, which supports the role of IST with ATG and CsA as treatment of choice for children with HAA without an HLA identical sibling donor.

Scheinberg,et al., 2011[9]

Background

In severe acquired aplastic anemia, hematopoietic failure is the result of immunemediated destruction of bone marrow stem and progenitor cells. Immunosuppressive therapy with antithymocyte globulin (ATG) plus cyclosporine is an effective alternative to stem-cell transplantation and improves blood counts and survival. Although horse ATG is the standard therapy, rabbit ATG is more potent in depleting peripheralblood lymphocytes and is preferred in other clinical circumstances.

Methods

From December 2005 through July 2010, we performed a randomized trial comparing these two ATG formulations in conventional regimens. Patients were treated at a single facility. The primary outcome was hematologic response at 6 months, as determined by blood counts. The study was designed to enroll 60 patients each for the rabbit-ATG and horse-ATG groups and was powered to detect a difference of 25 percentage points in the response rate.

Results

A large, unexpected difference was observed in the rate of hematologic response at 6 months in favor of horse ATG (68%; 95% confidence interval [CI], 56 to 80) as compared with rabbit ATG (37%; 95% CI, 24 to 49; P<0.001). Overall survival at 3 years also differed, with a survival rate of 96% (95% CI, 90 to 100) in the horse-ATG group as compared with 76% (95% CI, 61 to 95) in the rabbit-ATG group (P = 0.04) when data were censored at the time of stem-cell transplantation, and 94% (95% CI, 88 to 100) as compared with 70% (95% CI, 56 to 86; P = 0.008) in the respective groups when stem-cell–transplantation events were not censored.

Conclusions

In a randomized study, rabbit ATG was inferior to horse ATG as a first treatment for severe aplastic anemia, as indicated by hematologic response and survival. (Funded by the Intramural Research Program of the National Institutes of Health; ClinicalTrials.gov number, NCT00260689.)

3.5 ข้อมูลจากหลักฐานเชิงประจักษ์

3.5.1 Cochrane Library

จากการสืบค้นด้วยคำสำคัญ “aplastic anemia” หรือ “antithymocyte” หรือ “thymocyte” เมื่อวันที่ 20 มกราคม 2555 ไม่พบผลลัพธ์ที่เกี่ยวข้อง

3.5.2 BMJ Clinical Evidence

จากการสืบค้นด้วยคำสำคัญ “aplastic anemia” เมื่อวันที่ 20 มกราคม 2555 ไม่พบผลลัพธ์

3.5.3 NHS evidence

จากการสืบค้นด้วยคำสำคัญ “aplastic anemia” เมื่อวันที่ 20 มกราคม 2555 สรุปได้ดังนี้

All results = 1,159

Health Technology Assessments = 31 → related = 1 แต่ไม่สามารถอ่านได้เนื่องจากไม่ใช่ภาษาอังกฤษ

Systematic reviews = 12 → related = 1 (ซ้ำกับ Pubmed Gafter-Gvili, et al., 2008)

Practice guidelines = 85 → related = 1 (ซ้ำกับ Pubmed Marsh, et al., 2009)

3.5.4 Systematic reviews ซึ่งสืบค้นจาก Pubmed

ไม่ได้ทำการสืบค้นเพิ่มเติมเนื่องจากข้อมูลจาก 3.5.3 NHS evidence ให้ข้อสรุปที่ชัดเจนแล้ว

3.5.5 Randomized controlled trials ซึ่งสืบค้นจาก Pubmed

ไม่ได้ทำการสืบค้นเพิ่มเติมเนื่องจากข้อมูลจาก 3.5.3 NHS evidence ให้ข้อสรุปที่ชัดเจนแล้ว

3.6 ข้อมูลด้านค่าใช้จ่าย และการประเมินความคุ้มทางเศรษฐศาสตร์

ไม่ได้ทำการสืบค้น

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