7B

Please scan this QR code with your smartphone app to view an electronic version of this poster. If you don't have a smartphone, access the poster via the internet at: https://scientificpubs.congressposter.com/p/lvt1eeiw3swl81jg

Systematic Literature Review and Meta-Analysis on the Safety and Efficacy of Prophylactic Equine ATG Versus Comparators for Kidney Transplant

Barbara Mozejko-Pastewka[1], Erin Sheffels[2], Kevin Kallmes[2], Keith Kallmes[2], John Pederson[2], Raj Gokani[3], Andres Quintero[4], Judith Hey-Hadavi[4]

[1]Pfizer, Warsaw, Poland; [2]Nested Knowledge, St. Paul, MN, USA; [3]Pfizer, Walton Oaks, UK; [4]Pfizer, New York, NY, USA

BACKGROUND

- Renal transplantation is the gold standard for treating end-stage renal disease.[1]
- Preventing graft rejection, primarily through immunosuppressive therapy, is crucial.
- Anti-thymocyte globulins (ATG), derived from animals immunised with human lymphoid cells, play an important role in induction therapy for lymphocyte depletion.
- Equine ATG (eATG) and rabbit ATG (rATG) differ in terms of origin, production method and immunosuppressive profile. These differences translate into differences in antigen composition and may affect the efficacy and safety profiles of both ATGs.

OBJECTIVE

- To evaluate the effectiveness and safety of eATG, rATG and comparators in preventing rejection after kidney transplantation and the clinical implications based on available publications.

METHODS

Using the PubMed database, a PRISMA-compliant systematic review was performed of prospective comparative trials on the use of ATG for the prevention of kidney transplant rejection. We included all clinical trials and comparative studies of eATG or rATG, without restriction on publication date.

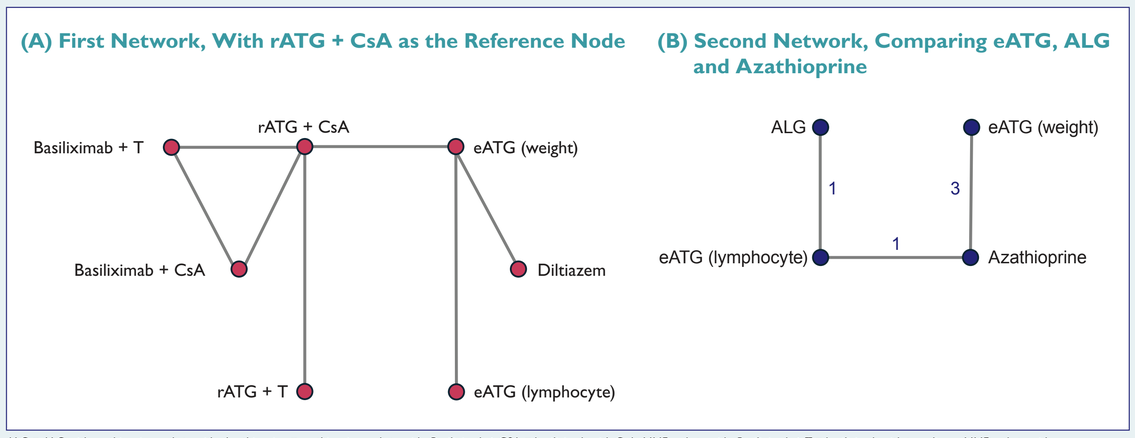
The following data were collected:

- **Patient demographics** including age, sex and immunological risk level.
- **Treatments** including living or deceased donor and ATG by dosing strategy (i.e., weight- vs. lymphocyte-based dosing [W-dosing vs L-dosing respectively]) as well as comparators.
- **Outcomes** including freedom from rejection, acute rejection, graft survival, graft function metrics, infection and mortality.

The following analyses were performed:

- **Hierarchical random-effects network meta-analysis (NMA)** of randomised controlled trials on 2 independent networks (**Figure 1**).
- **Effect sizes** reported as incidence rate ratios (IRRs).
- **Differences between treatments** in the network (considered significant if the 95% confidence intervals did not overlap).
- **P-scores** indicate the certainty (overall probability) that one treatment group performed better than another treatment group, averaged over all competing treatments in the network.
  - A higher P-score indicates the treatment may perform better than treatments with lower P-scores in the network.

Figure 1. Network Diagrams Showing Interventions and Comparators for Studies Included in the Network Meta-Analysis



ALG = ALG with azathioprine and steroids; Azathioprine = azathioprine and steroids; Basiliximab + CSA = basilizimab with CsA, MMF and steroids; Basiliximab + T = basilizimab with tacrolimus, MMF and steroids; Diltiazem = diltiazem with CsA, azathioprine and steroids; eATG (lymphocyte) = lymphocyte-based eATG with CsA, azathioprine and steroids; eATG (weight) = weight-based eATG with CsA, azathioprine and steroids; rATG + CsA = weight-based rATG with CsA, azathioprine and steroids; rATG + T = weight-based rATG with tacrolimus, MMF and steroids.

RESULTS

Literature Search

- Out of 3026 records identified, 11 studies were included in the NMA comparing eATG (publication years 1973-2001) and comparator treatments, including combinations of rATG, monoclonal antibodies (mABs), azathioprine (AZA), methotrexate (MTX), cyclosporine-A (CsA), glucocorticoids (GC), tacrolimus and mycophenolate mofetil (MMF).
- The first NMA (**Figure 1A**, comprising 746 patients) compared W-dosing vs L-dosing eATG regimens (119 patients, cumulatively) to W-dosed rATG (417 patients), and non-ATG therapies (210 patients).[2-6] The background therapy was CsA/AZA/GC, and the reference treatment was W-dosed rATG plus CsA/AZA/GC.
- The second network (**Figure 1B**, comprising 260 patients) compared W-dosing vs L-dosing eATG regimens (131 patients) to drug combinations without ATG.[7-11] The background therapy was AZA/GC, and the reference was background therapy alone.

Network Meta-analysis

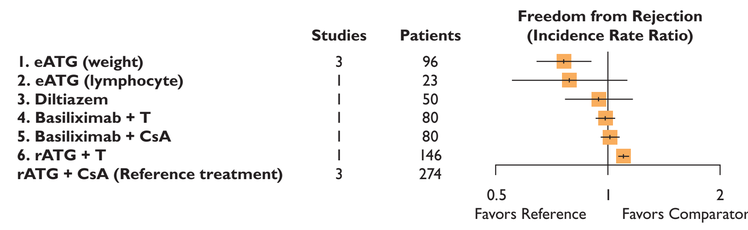
- Efficacy: findings on freedom from rejection.
  - Graft rejection
    - **First Network:** W-dosed eATG patients had significantly lower reported freedom from rejection and higher acute rejection than rATG. L-dosing eATG also reported a higher acute rejection compared to rATG, without significant differences in freedom from rejection (**Figure 2A**).
    - **Second Network:** W-based eATG nonsignificant (n.s.) different incidence of freedom from rejection or acute rejection compared to non-ATG treatment (**Figure 2B**). L-dosed eATG n.s. different incidence of freedom from rejection.
  - Graft failure
    - **First Network:** Differences between rATG and eATG for graft failure.
    - **Second Network:** L-dosed eATG resulted in a significantly lower risk of graft failure. W-dosed eATG n.s. different risks of graft failure compared to non-ATG treatment.
- Safety
  - Infection
    - **First Network:** W-dosed eATG led to significantly higher incidence of infection compared to rATG patients. L-dosed eATG n.s. differences in infection (**Figure 3A**).
    - **Second Network:** Both eATG groups experienced a significantly higher incidence of infection relative to the non-ATG comparator (**Figure 3B**).
  - Mortality
    - There were no significant differences in mortality in either network.

Key Findings

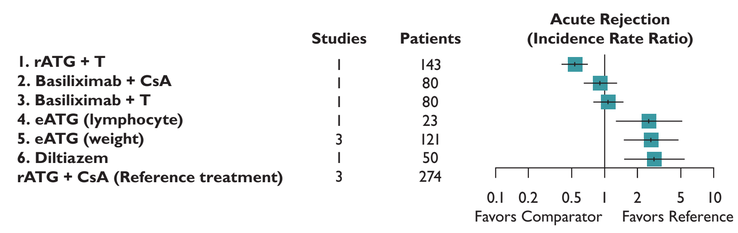
- Efficacy: L-dosed eATG has comparable efficacy to W-dosed rATG.
- Safety
  - ATG-based treatments reported higher incidence of infection compared to non-ATG treatments.
  - W-dosed eATG has higher incidence of infection compared to W-dosed rATG with the same background treatment.
  - ATG-based treatments showed no differences in incidence of mortality.

Figure 2. Forest Plots Showing Rates of Freedom From Rejection and Acute Rejection Across Interventions and Comparators

(A) Freedom From Rejection and Acute Rejection: First Network

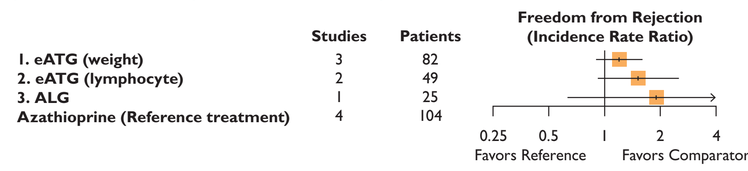


	Studies	Patients	IRR	95% CI	P-score
1. eATG (weight)	3	96	0.76	[0.64, 0.90]	0.069
2. eATG (lymphocyte)	1	23	0.79	[0.55, 1.13]	0.178
3. Diltiazem	1	50	0.95	[0.77, 1.17]	0.475
4. Basiliximab + T	1	80	0.99	[0.93, 1.04]	0.499
5. Basiliximab + CsA	1	80	1.01	[0.96, 1.07]	0.698
6. rATG + T	1	146	1.10	[1.07, 1.14]	0.981
rATG + CsA (Reference treatment)	3	274			

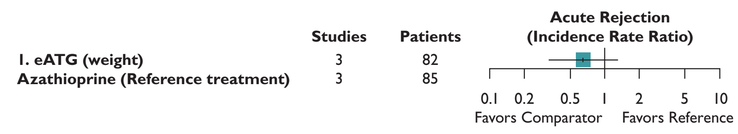


	Studies	Patients	IRR	95% CI	P-score
1. rATG + T	1	143	0.53	[0.41, 0.70]	0.999
2. Basiliximab + CsA	1	80	0.92	[0.65, 1.29]	0.755
3. Basiliximab + T	1	80	1.08	[0.79, 1.48]	0.575
4. eATG (lymphocyte)	1	23	2.55	[1.28, 5.10]	0.215
5. eATG (weight)	3	121	2.67	[1.51, 4.72]	0.185
6. Diltiazem	1	50	2.86	[1.52, 5.38]	0.106
rATG + CsA (Reference treatment)	3	274			

(B) Freedom From Rejection and Acute Rejection: Second Network



	Studies	Patients	IRR	95% CI	P-score
1. eATG (weight)	3	82	1.20	[0.90, 1.60]	0.440
2. eATG (lymphocyte)	2	49	1.52	[0.92, 2.51]	0.689
3. ALG	1	25	1.90	[0.63, 5.72]	0.777
Azathioprine (Reference treatment)	4	104			



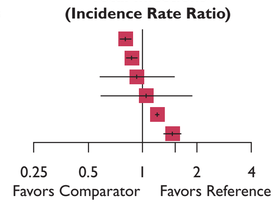
	Studies	Patients	IRR	95%-CI	P-score
1. eATG (weight)	3	82	0.65	[0.33, 1.30]	0.886
Azathioprine (Reference treatment)	3	85			

Caution: Differences in outcomes across treatment arms may be attributed in part or entirely to differences in background therapy or interactions, not necessarily to differences in exposure to main comparator.

Basiliximab + CSA = basilizimab with CsA, MMF, and steroids; Basiliximab + T = basilizimab with tacrolimus, MMF, and steroids; Diltiazem = diltiazem with CsA, azathioprine, and steroids; eATG (lymphocyte) = lymphocyte-based eATG with CsA, azathioprine, and steroids; eATG (weight) = weight-based eATG with CsA, azathioprine, and steroids; rATG +CsA = weight-based rATG with CsA, azathioprine, and steroids; rATG + T = weight-based rATG with tacrolimus, MMF, and steroids.

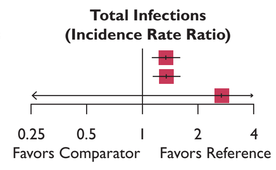
Figure 3. Forest Plots Showing Rates of Infection Across Interventions and Comparators

(A) Total Infection Rate: First Network



	Studies	Patients	IRR	95% CI	P-score
1. Basiliximab + CsA	1	80	0.80	[0.75, 0.86]	0.920
2. Basiliximab + T	1	80	0.87	[0.81, 0.93]	0.729
3. Diltiazem + background 1	1	50	0.93	[0.58, 1.49]	0.623
4. eATG (lymphocyte)	1	23	1.05	[0.59, 1.88]	0.469
5. rATG + T *	1	146	1.21	[1.19, 1.23]	0.243
6. eATG (weight)	3	96	1.46	[1.31, 1.64]	0.026
rATG + CsA (Reference treatment)	3	274			

(B) Total Infection Rate: Second Network



	Studies	Patients	IRR	95% CI	P-score
1. eATG (lymphocyte)	2	49	1.35	[1.14, 1.61]	0.398
2. eATG (weight)	1	36	1.36	[1.15, 1.61]	0.387
3. ALG	1	25	2.71	[0.14, 51.49]	0.300
Azathioprine (Reference treatment)	2	60			

Caution: Differences in outcomes across treatment arms may be attributed in part or entirely to differences in background therapy or interactions, not necessarily to differences in exposure to main comparator.

Basiliximab + CSA = basilizimab with CsA, MMF, and steroids; Basiliximab + T = basilizimab with tacrolimus, MMF, and steroids; Diltiazem = diltiazem with CsA, azathioprine, and steroids; eATG (lymphocyte) = lymphocyte-based eATG with CsA, azathioprine, and steroids; eATG (weight) = weight-based eATG with CsA, azathioprine, and steroids; rATG +CsA = weight-based rATG with CsA, azathioprine, and steroids; rATG + T = weight-based rATG with tacrolimus, MMF, and steroids.

DISCUSSION

- **Interpretation of Results**
  - W-dosing eATG treatment led to significantly higher rates of rejection and infection compared to W-dosing rATG treatment.
  - L-dosing eATG treatment had comparable outcomes to W-dosing rATG treatment, indicating L-dosing eATG treatment may be a treatment option for renal transplant patients.
  - Whilst ATGs led to significantly higher incidence of infection, no significant differences in mortality were found between any of the ATG treatments vs reference treatments.
- **Limitations**
  - Dated studies - all eATG studies precede 2001 and rATG studies 2012.
  - High heterogeneity in induction regimens and population characteristics, including immunological risk.
  - Advancements in the standard of care for transplant recipients may have resulted in enhanced graft effectiveness, survival rates and safety parameters in contemporary studies compared to historical data.

CONCLUSIONS

- **Summary of Findings**
  - Preventing graft rejection, primarily through immunosuppressive therapy, is crucial for successful kidney transplantation.
  - This systematic review and network metanalysis evaluated eATG, rATG and comparators in 11 studies in kidney transplant patients.
  - L-dosing eATG reported similar outcomes, except with respect to acute rejection; however, W-dosing eATG treatment was reported to be less effective compared to rATG.
- **Recommendations**
  - Further analysis of registry data is recommended to validate these findings and address standard of care. Additional comparative studies are warranted.

REFERENCES

1. Abecassis M, et al. *CJASN* 2008;3:471-80. **2.** Abouna GM, et al. *Transplantation* 1995;59:1564-8. **3.** Brennan DC, et al. *Transplantation* 1999;67:1011-8. **4.** Hernández D, et al. *Transplantation* 2007;84:706-14. **5.** Kasiske BL, et al. *Am J Kidney Dis* 1997;30:639-45. **6.** Vacher-Coponat H, et al. *Transplantation* 2012;93:437-43. **7.** Chatterjee SN. *Arch Surg* 1976;111:680-3. **8.** Kreis H, et al. *Kidney Int* 1981;19:438-44. **9.** Toledo-Pereyra LH, et al. *Transplantation* 1985;40:448-50. **10.** Turcotte JG, et al. *Arch Surg* 1973;106:484-8. **11.** Wechter WJ, et al. *Transplantation* 1979;28:365-7.

DISCLOSURES

Barbara Możejko-Pastewka, Raj Gokani, Judith Hey-Hadavi, Andres Quintero are employees of Pfizer and may hold share/stock options. Erin Sheffels, Kevin Kallmes, Keith Kallmes, John Pederson are employees of Nested Knowledge

This study was sponsored by Pfizer. Editorial support was provided by Engage Scientific Solutions, funded by Pfizer, and consisted solely of copyediting and poster formatting; no contribution was made to content.

Presented at the joint Banff Foundation for Allograft Pathology and the Paris Institute for Transplantation and Organ Regeneration (BANFF-PITOR) Congress, Paris, France, 16–20 September 2024