A T-cell positive, B-cell negative allogeneic flow crossmatch with a double-negative autologous flow crossmatch: Interference of therapeutic brodalumab in a patient with psoriasis

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Case presentation

A 60 year old male patient was evaluated for his first kidney transplant. The patient had no history of transfusions and his flow PRA and LSA results showed no detectable HLA antibodies (0% PRA). The patient was tested against a class I and II mismatched, ABO-compatible living unrelated donor and a routine flow crossmatch was performed. The results showed a T-cell positive but B-cell negative crossmatch, which is considered inconclusive. A closer look into the patient's clinical history showed that he was prescribed brodalumab to treat his psoriasis.

Results

Our flow crossmatch is routinely performed with pronase-treated donor cells. To exclude pronase interference, the flow crossmatch was repeated with untreated donor cells. Again, the results showed a T-cell positive but B-cell negative crossmatch. A surrogate crossmatch against another, ABO-compatible, HLA class I mismatched donor also resulted in a T-cell positive but B-cell negative crossmatch, indicating a general reactivity against allogeneic T cells. However, the autologous flow crossmatch was negative for both T cells and B cells, which was unexpected at first. Furthermore, the serum from 2024-04-04 was repeatedly tested negative against donor T cells and B cells.

Interpretation

Because this patient was treated with brodalumab, we looked into the mechanism of this therapeutic antibody and its possible interference with the crossmatch results. Brodalumab is a human monoclonal IgG_2 antibody that targets the IL-17 receptor subunit A (IL-17RA). IL-17RA is found on a variety of cell types including T cells. Our fluorescent secondary anti-IgG antibody used in the crossmatch will bind to the therapeutic antibody (Figure1). We infer that the positive T cell crossmatch is directly caused by brodalumab because when he misses an injection and the therapeutic antibody is below an effective concentration (Figure 2) then his serum does not cause a positive T cell reaction. While this may explain the T-cell positive flow crossmatches for the donor and the surrogate, we would have also expected a T cell positive autologous flow crossmatch. However, our CD3+ marker for the flow crossmatch cannot differentiate between the different T cell subpopulations. An absolute lymphocyte cell count of the patient for CD19+ (B cell marker), CD4+ (T helper cells), CD8+ (cytotoxic T cells), and CD16+/CD56+ (NK cells) was in the normal range. We hypothesize that the continuous exposure of the patient's immune cells to brodalumab lead to a reduction of IL-17RA on their cell surface, thereby resulting in a negative auto-crossmatch. Taken together, it was determined that the positive T-cell flow crossmatch test results were not a contraindication to transplant.

Figure 1

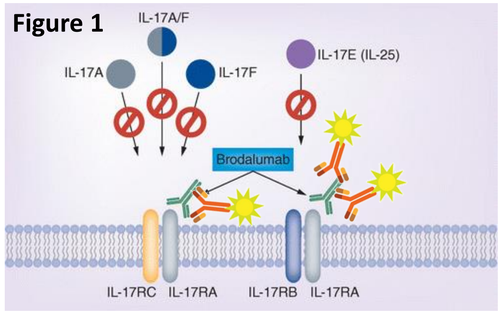

Figure 1. Brodalumab is a human monoclonal IgG_2 antibody that binds to IL-17RA found on T cells. Our fluorescent secondary anti-IgG antibody will bind to brodalumab. Adapted from [1].

Figure 2

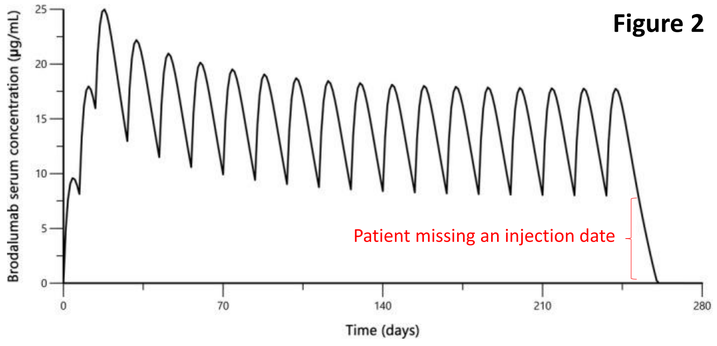

Figure 2. Brodalumab is given weekly to stay within the therapeutic range. Because of the short half life, the concentration drops to low concentrations if the patient misses an injection. Adapted from [2].

Donor FCXM	T Cells			B cells		
Pronase treated	MCV	MCS	Result	MCV	MCS	Result
Negative ctrl	169	-	-	226	-	-
Positive ctrl MHC class II	142	-27	Negative	565	339	Positive
Positive ctrl MHC class I + II	432	263	Positive	592	366	Positive
Recipient serum 2024-04-16	282	113	Positive	248	22	Negative
Recipient serum 2024-04-04	153	-16	Negative	212	-14	Negative
Recipient serum 2023-12-20	275	106	Positive	243	17	Negative
Recipient serum 2021-11-29	276	107	Positive	240	14	Negative

Donor FCXM	T Cells			B cells		
Untreated	MCV	MCS	Result	MCV	MCS	Result
Negative ctrl	199	-	-	355	-	-
Positive ctrl MHC class II	190	-9	Negative	552	197	Positive
Positive ctrl MHC class I + II	423	224	Positive	659	304	Positive
Recipient serum 2024-04-16	299	100	Positive	357	2	Negative
Recipient serum 2024-04-04	192	-7	Negative	355	0	Negative
Recipient serum 2023-12-20	292	93	Positive	358	3	Negative
Recipient serum 2021-11-29	293	94	Positive	346	-9	Negative

Surrogate FCXM	T Cells			B cells		
Pronase treated	MCV	MCS	Result	MCV	MCS	Result
Negative ctrl	150	-	-	167	-	-
Positive ctrl MHC class II	135	-15	Negative	561	394	Positive
Positive ctrl MHC class I + II	439	289	Positive	607	440	Positive
Recipient serum 2024-04-16	232	82	Positive	169	2	Negative
Recipient serum 2024-04-04	139	-11	Negative	141	-26	Negative
Recipient serum 2023-12-20	222	72	Weak Positive	165	-2	Negative
Recipient serum 2021-11-29	235	85	Positive	169	2	Negative

Auto FCXM	T Cells			B cells		
Pronase treated	MCV	MCS	Result	MCV	MCS	Result
Negative ctrl	180	-	-	217	-	-
Positive ctrl MHC class II	159	-21	Negative	526	309	Positive
Positive ctrl MHC class I + II	392	212	Positive	631	414	Positive
Recipient serum 2024-04-16	185	5	Negative	197	-20	Negative
Recipient serum 2024-04-04	164	-16	Negative	192	25	Negative
Recipient serum 2023-12-20	179	-1	Negative	193	-24	Negative
Recipient serum 2021-11-29	188	8	Negative	199	-18	Negative

T-Cells MCV	SD	B-cells MCV	SD
150-204	27	194-260	33

Conclusion

Therapeutic antibody treatment may belong to the standard of care for a variety of diseases that are not directly linked to solid organ transplantation. Therefore, flow crossmatch results of patients that receive any type of antibody therapy need to be carefully examined to make an informed decision on the risk for transplant rejection.

References

[1] Kivelevitch DN, Menter A. Use of brodalumab for the treatment of psoriasis and psoriatic arthritis. Immunotherapy. 2015;7(4):323-33.

[2] Timmermann S, Hall A. Population pharmacokinetics of brodalumab in patients with moderate to severe plaque psoriasis. Basic Clin Pharmacol Toxicol. 2019 Jul;125(1):16-25.