Management of Drug-drug interactions

Evidence-based Medicine | Official Recommendations | Expert opinion

The initiation of abatacept therapy in combination with conventional DMARDs or after the use of other biologics continues to raise many questions regarding potential drug-drug interactions. Data from clinical trials led to the recommendation that abatacept should be used in combination with methotrexate. However, these data also showed that abatacept in combination with another conventional DMARD seems effective and raises no major safety issues. In addition, various results indicate that methotrexate, NSAIDs, and glucocorticoids have no influence on the pharmacokinetics of abatacept. Finally, combined use of abatacept and another biologic agent, most notably a TNF antagonist, is associated with an increased risk of serious adverse events and therefore is not recommended.

Abatacept combined with conventional disease-modifying antirheumatic drugs (DMARDs)

- Several studies, notably the extension phase of the AIM study (Abatacept in Inadequate responders to methotrexate), established the efficacy and safety of abatacept combined with methotrexate in a mean dose of 15 mg/week (65, 66). When methotrexate is contraindicated or poorly tolerated, the efficacy and safety of combining another conventional disease-modifying drug with abatacept must be considered.

- In the ASSURE study (Abatacept Study of Safety in Use with other Rheumatoid arthritis therapies) (32), patients received either abatacept or a placebo while continuing previous conventional DMARDs or biologics. An analysis of subgroups defined based on the concomitant DMARD (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, gold, or azathioprine) showed that these drugs had a good overall safety profile when used with abatacept. A higher rate of adverse events with the DMARD was seen only with leflunomide (23.6% in the abatacept group and 15.3% in the placebo group). The most commonly reported adverse events were severe infections and muscle and connective tissue complaints (Table 4).

Table 4 – ASSURE study: Serious adverse events reported in the groups given abatacept and those given DMARDs only (32)

	placebo + DMARD n=418	abatacept + DMARD n=856
Serious adverse events	12.2%	11.7%
Serious infections	1.7%	2.6%
· Serious respiratory tract infections	1.0%	1.1%
· Serious urinary tract infections	0.2%	0.5%
Solid cancer	3.8%	3.2%
· Basal-cell carcinoma	0.7%	0.4%

Recommendations about abatacept and conventional DMARDs

In patients with RA, abatacept in combination with methotrexate has been found more effective in improving disease activity and decreasing 5-year structural damage than methotrexate alone (67). Therefore, methotrexate is the recommended DMARD for combination with abatacept. However, when methotrexate is contraindicated or poorly tolerated, another DMARD can be used, preferably a drug with proven structural effects. In the current state of our knowledge, when a concomitant DMARD is used, there is no evidence to suggest a need for adjusting the dosage of the DMARD. The recommended starting dosage of methotrexate is 15 mg/week; this dosage may be decreased in the event of a prolonged remission without evidence of structural progression.

Use of abatacept in monotherapy

In the event of intolerance to all available DMARDs, treatment with abatacept in monotherapy may be considered. In a pilot study (68), abatacept was given 1 month after DMARD discontinuation, in a dosage of 0.5, 2, or 10 mg/kg. The ACR response rates at day 85 (3 months) were higher in the abatacept groups than in the placebo group, and the highest ACR20 response rate occurred with the dosage usually given in clinical practice (10 mg/kg) (Table 5).

Table 5 - Proportions of patients achieving ACR20, 50, and 70 criteria at day 85 in the treatment groups: abatacept in monotherapy in a dosage of 0.5, 2, or 10 mg/kg and in the placebo group (68)

% ACR responders on D85	placebo n=32	abatacept 0,5 mg/kg n=26	abatacept 2 mg/kg n=32	abatacept 10 mg/kg n=32
ACR20 (primary criterion)	31%	23%	44%	53%
ACR50	6%	0	19%	16%
ACR70	0	0	12%	6%

Combining abatacept with an antiinflammatory drug and/or analgesic

To date, there is no published data suggesting that intolerance to abatacept may be increased by concomitant use of a glucocorticoid, nonsteroidal antiinflammatory drug (NSAID), and/or analgesic adversely.

Pharmacokinetic interactions

Pharmacokinetic data have shown that methotrexate, NSAIDs, and glucocorticoids have no effect on the clearance of abatacept. Therefore, NSAIDs, glucocorticoids, and analgesics can be used concomitantly with abatacept.

Abatacept combined with another biologic agent

Studies have evaluated the efficacy and safety of abatacept used in combination with other biologic agents such as anti- TNF agents or IL-1Ra (anakinra) (32, 33). Based on their results, combining abatacept with another biological agent, most notably a TNF antagonist, is not recommended, given the important increase in infections and malignancies (Table 6). In contrast, no opportunistic infection was reported.

Table 6 – *Serious adverse events reported in patients treated with abatacept combined with another biologic agent vs patients treated with another biologic agent in the ASSURE study (32)*

	placebo + biotherapy* n=64	abatacept + biotherapy* n=103
Serious adverse events	12.5%	22.3%
Serious infections	1.6%	5.8%
· Serious respiratory tract infections	1.6%	2.9%
· Serious urinary tract infections	0%	1.9%
Solid cancer	1.6%	6.8%
· Basal-cell carcinoma	0%	1.9%

*biotherapy = TNF antagonist or anakinra

Abatacept/ TNF antagonist

The ARRIVE study (69) assessed the efficacy and safety of abatacept initiated immediately after TNF antagonist discontinuation or 2 months later. Adverse event rates were similar in both groups, regardless of a 2-month washout period. In practice, after discontinuation the TNF antagonist, abatacept can be started on the day the next dose of TNF antagonist was scheduled, except in highly selected situations. In patients at high risk for infections, a washout period equal to 5 times the half-life of the TNF antagonist before starting abatacept therapy may deserve consideration.

Abatacept/anakinra

The results of the ASSURE study (32) and previously published data (70) in 4 children with juvenile

idiopathic arthritis who benefited markedly from abatacept combined with anakinra therapy were not evaluated throroughly regarding the efficacy and safety of this combination. Consequently, this combination is not recommended.

- **After rituximab therapy**

Few data are available on this combination (71). Concomitant inhibition of both the T-cell and the B-cell populations raises theoretical concerns regarding the tolerance of these combined biologic therapies abatacept and rituximab. In the current state of our knowledge, concomitant use of abatacept and rituximab is not recommended.

- After rituximab therapy

When abatacept therapy is considered in a patient previously treated with rituximab, the risk/benefit ratio should be evaluated carefully. An immunoglobulin assay by weight and lymphocyte phenotype determination evaluating restoration of the B-cell population may help to assess the risk of infection. A new biologic other than a TNF antagonist should not be introduced within the first 24 weeks after a rituximab course.

The prospective ORA registry included 179 patients who received abatacept therapy after rituximab therapy. The median interval between the last rituximab dose and the first abatacept dose was 8 months. After a median of 28 weeks (86 patient-years) of abatacept therapy, 40 (7.7%) patients had stopped abatacept because of serious adverse events, 71.8% because of inadequate effectiveness, and 20.5% for other reasons (e.g., adverse event and inadequate effectiveness or patient request) (72).

- Rituximab after abatacept therapy

Rituximab initiation can be considered 8 weeks after the last abatacept infusion. There is no practical test to assess immunological recovery after abatacept therapy.

- **Abatacept/tocilizumab**

No data on the efficacy and safety of this combination are available. Consequently, concomitant abatacept and tocilizumab therapy is currently not recommended.

- **Abatacept/denosumab**

Osteoclasts interact with T cells via the RANK (Receptor Activator of Nuclear factor Kappa b)/RANK-Ligand system, which generates a signal stimulating osteoclast differentiation. Studies show that CTLA4 can bind directly to osteoclast precursors, thereby inhibiting mononuclear cell differentiation to osteoclasts (73). The hypothesis for CTLA4-Ig to have anti-osteoclast properties may explain the prevention of bone erosions during abatacept therapy in RA. However, no data are available on the combined use of abatacept and denosumab, which might alter calcium metabolism (risk of hypocalcaemia?) and consequently this combination is not recommended.